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THE CURRENT STATUS OF FLEXIBLE FIBEROPTIC ENDOSCOPY

JEROME D. WAYE, M.D.
Guest Editor

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CONTENTS OF VOLUME 42

NUMBER 1, JANUARY–FEBRUARY 1975

The Current Status of Flexible Fiberoptic Endoscopy

COLONOSCOPY: A CLINICAL VIEW. *Jerome D. Waye, M.D.* 1
ENDOSCOPIC VISUALIZATION OF THE PANCREATIC AND BILIARY DUCTS. *Jerome D. Waye, M.D.* 35
THE CURRENT STATUS OF ESOPHAGOSCOPY, GASTROSCOPY, AND DUODENOSCOPY. *Jerome D. Waye, M.D.* 57
APPLICATION OF THE FLEXIBLE BRONCHOSCOPE. *Alvin S. Teirstein, M.D., Ming Chuang, M.D., and Albert Miller, M.D.* 81

NUMBER 2, MARCH–APRIL 1975

OBITUARY: DR. RALPH COLP 95
EVERY STEP OF THE WAY. *Lawrence J. Roose, M.D. and Howard D. Zucker, M.D.* 99
THE LUNG IN SYSTEMIC LUPUS ERYTHEMATOSUS: A CLINICO-PATHOLOGIC STUDY OF 20 CASES. *A. Olusegun Fayemi, M.D.* 110
ISCHEMIC COLITIS WITH PERFORATION INTO THE GALL BLADDER. *Peter J. Wilk, M.D.* 119
A HISTOLOGIC CHRONOLOGY OF THE CLINICAL COURSE OF THE KERATOCARCINOMA (SO-CALLED KERATOACANTHOMA). *John Kwittken, M.D.* 127
PREOPERATIVE DIAGNOSIS OF THE MECKEL'S DIVERTICULUM BY SEQUENTIAL 99M TECHNETIUM PERTECHNETATE SCANNING. *Hee Kyung Lee, M.D., Ira S. Schwartz, M.D., Thomas Nipper, M.D., Gadi Grichon, M.D., and A. Robert Beck, M.D.* 136
CLINICAL STUDIES WITH CEFAZOLIN: A NEW CEPHALOSPORIN ANTIBIOTIC. *Glenn S. Hammer, M.D., Bruce S. Ribner, M.D., Burt R. Meyers, M.D., and Shalom Z. Hirschman, M.D.* 142
THE RESPIRATORY DISTRESS SYNDROME AND GLUCOCORTICOID TREATMENT: THE CASE FOR ENZYME INDUCTION. *David M. Nathan, B.A.* 150
NEUROLOGIC NOTES. *John Lusins, M.D., Editor* 167
    A GUILLAIN-BARRÉ VARIANT: OPHTHALMOPLEGIA, ATAXIA AND AREFLEXIA. *By Michael J. Davis, M.D.* 167
UNUSUAL PROBLEMS IN SURGERY. *A. Robert Beck, M.D., Editor*
    BOCHDALEK HERNIA PRESENTING AT ONE YEAR OF AGE 173

NUMBER 3, MAY–JUNE 1975

OBITUARY: DR. GORDON D. OPPENHEIMER 177
TREATMENT OF HEMORRHOIDS AND APPLICATION OF CRYOTECHNIQUE. *Changyul Oh, M.D.* 179

CARCINOMA OF THE BREAST OCCURRING IN A HUSBAND AND WIFE: A BRIEF COMMUNICATION. *Bernard Bruce Wetchler, M.D. and Barry Simon, M.D.* ... 205
THYROID CARCINOMA PRESENTING AS EPIDURAL METASTASIS WITH SPINAL CORD COMPRESSION. *Robert A. Brodner, M.D., A. J. Berman, M.D., Marian Wisniewski, M.D., and Hiroshi Nakagawa, M.D.* ... 207
DISTURBANCES OF PSYCHOSEXUAL DEVELOPMENT OF ADOLESCENT GIRLS. *Fred Brown, Ph.D.* ... 216
AIDS TO THE SURGEON BY MAMMOGRAPHY. *Albert S. Lyons, M.D.* ... 223
CHONDROBLASTIC SARCOMA OF THE BREAST. *Susan D. Gisser, M.D. and Cyril Toker, M.D.* ... 232
THE VALUE OF EXPLORATORY LAPAROTOMY IN FEVER OF UNKNOWN ETIOLOGY. *Sharon Wilkinson, B.A.* ... 236
MODERN CONCEPTS IN THE MANAGEMENT OF GASTROJEJUNOCOLIC FISTULA. *John Hodgson, M.D., Oswaldo F. Medina, M.D., Marin Teodorescu, M.D., and Abba A. Messe, M.D.* ... 239
NEUROLOGIC-NEUROSURGICAL NOTES. *John Lusins, M.D. and Martin H. Savitz, M.D., Coeditors*
  VON HIPPEL-LINDAU'S DISEASE: CASE REPORT AND ONCOGENIC CONSIDERATION. *By Yong-Myun Rho, M.D., Ved P. Sachdev, M.D., and Leonard I. Malis, M.D.* ... 245
THE STUDENT'S CORNER. *Jeffrey Backner, B.S., Editor* ... 252

NUMBER 4, JULY–AUGUST 1975

Alan F. Guttmacher Memorial Issue

Joseph J. Rovinsky, M.D. and Christopher Tietze, M.D.
Guest Editors

PART I

EDITORS' NOTE ... 255

POPULATION AND FAMILY PLANNING

FAMILY PLANNING AND MALARIA CONTROL: Some Parallels between Two Large-Scale Health-Related Programs. *Richmond K. Anderson, M.D., Ph.D.* ... 256
POPULATION GROWTH AND THE QUALITY OF LIFE. *Allan C. Barnes, M.D.* ... 265
ON FAMILY PLANNING ASSOCIATIONS AND DEVELOPMENT OF POPULATION POLICY AND PROGRAMS. *Leslie Corsa, M.D., M.P.H.* ... 269
MATERNAL AND CHILD HEALTH AND FAMILY PLANNING SERVICES: The Contemporary Global Picture, *Edwin M. Gold, M.D.* ... 277
KNOWLEDGE, PERCEPTION, AND CHANGE: Notes on a Fragment of Social History. *Frederick S. Jaffe* ... 286
ALAN GUTTMACHER, AND FAMILY PLANNING IN CUBA, 1966 AND 1974. *Irwin H. Kaiser, M.D., Ph.D.* ... 300

RECRUITING THE UNCOMMITTED LEADER FOR FAMILY PLANNING. *Thomas S. Moulding, M.D., Charles F. Cortese, Ph.D., and John C. Cobb, M.D., M.P.H.* 308
FINANCIAL ASSURANCE FOR REPRODUCTIVE HEALTH SERVICES. *Charlotte Muller, Ph.D.* 316
NATURAL LAW AND PLANNED PARENTHOOD. *Malcolm Potts, M.B., B.Ch., Ph.D., D.O.* 326
DR. ALAN F. GUTTMACHER: As Remembered by a Latin American Physician. *Benjamin Viel, M.D., M.P.H.* 335

METHODS OF FERTILITY REGULATION

EXPERIENCE WITH INTRAUTERINE CONTRACEPTION BY ADOLESCENT WOMEN. *Mary E. Lane, M.D. and Aquiles J. Sobrero, M.D.* 337
ERNST GRÄFENBERG AND HIS RING. *Hans Lehfeldt, M.D.* 345
THE LOOP DECADE. *Jack Lippes, M.D., and Maria Zielezny, Ph.D.* 353
"AND SO ON" *Ronald J. Pion, M.D.* 364
PROSTAGLANDINS IN CONCEPTION CONTROL. *Harold Schulman, M.D.* 367
ADVANCES AND OPPORTUNITIES IN FERTILITY RESEARCH. *Sheldon J. Segal, Ph.D.* 375
DISCONTINUATION OF THE PILL AND THE IUD IN THE UNITED STATES: 1960–1970. *Charles F. Westoff, Ph.D. and Elise F. James, M.A.* 384

NUMBER 5, SEPTEMBER–OCTOBER 1975

Alan F. Guttmacher Memorial Issue

Joseph J. Rovinsky, M.D. and Christopher Tietze, M.D.
Guest Editors

PART II (*The first part appeared in the July–August issue*)

THE ART AND SCIENCE OF MEDICINE

ADVANCES IN UNDERSTANDING THE EFFECTS OF VASECTOMY. *Joseph E. Davis, M.D. and Ira Lubell, M.D., M.P.H.* 391
DIABETES MELLITUS IN PREGNANCY. *John W. Greene, Jr., M.D.* 398
IMMUNOCHEMISTRY OF A REPRODUCTIVE ANTIGEN INVOLVED IN STERILITY AND FERTILITY. *Seymour Katsh, Ph.D., Frederick W. Leaver, Ph.D., and Grace F. Katsh, Ph.D.* 405
AMYLOPHAGIA DURING PREGNANCY: Some Maternal and Perinatal Correlations. *Donald Keith, M.B.A., Louis Keith, M.D., Gary S. Berger, M.D., James Foot, M.A., and Augusta Webster, M.D.* 410
PRODUCTION OF DISSEMINATED INTRAVASCULAR COAGULATION IN MONKEYS BY INJECTION OF CELL-FREE EXTRACTS OF PLACENTAS. *Eberhard Mueller-Heubach, M.D., Karlis Adamsons, M.D., Ph.D., and Ronald E. Myers, M.D., Ph.D.* 415
MODERN USE OF THE LAMINARIA TENT. *Kenneth R. Niswander, M.D.* 424

PSYCHOSOCIAL CONSIDERATIONS

HUMANE ABORTION SERVIEWS: A REVOLUTION IN HUMAN RIGHTS AND THE DELIVERY OF A MEDICAL SERVICE. *Michael S. Burnhill, M.D., D.M.Sc.* 431

THERAPEUTIC LISTENING: An Adolescent Guidance Program in Motivation for Contraception. *S. B. Gusberg, M.D., Stanley Marinoff, M.D., Jesse Hilsen, M.D., Louis Cox, Ph.D., Alma Young, M.S.W., and Olive Cameron, R.N.* 439

ALAN F. GUTTMACHER, M.D.: His Role in Teaching Human Sexuality. *George J. Langmyhr, M.D. and Harold I. Lief, M.D.* 445

THE NEED FOR COMPREHENSIVE PROGRAMS FOR SCHOOL AGE PARENTS. *John B. Nettles, M.D., Lois H. Gatchell, George W. Prothro, M.D., Sara R. De Persio, M.D., M.P.H., and Eve Ann Marvin, M.A.* 452

PSYCHOSOCIAL ASPECTS OF ABORTION IN THE UNITED STATES. *Joy D. Osofsky, Ph.D., Howard J. Osofsky, M.D., Renga Rajan, M.D., and Deborah Spitz, B.A.* 456

THE IMPACT OF VOLUNTARY ABORTION ON AMERICAN OBSTETRICS AND GYNECOLOGY. *Donald P. Swartz, M.D.* 468

INFANT MORTALITY IN SWEDEN—IMPLICATIONS FOR THE UNITED STATES. *Helen M. Wallace, M.D. and Hyman Goldstein, Ph.D.* 479

NUMBER 6, NOVEMBER–DECEMBER 1975

EDITORIAL. SALUTE TO DR. STEVEN PODOS 501

EGAS MONIZ, PIONEER OF ANGIOGRAPHY AND LEUCOTOMY. *António R. Damásio, M.D.* 502

CLOUD NINE ACADEME AND THE TRENCHES OF HEALTH ADMINISTRATION. *Lowell Eliezer Bellin, M.D., M.P.H.* 514

TWIN GESTATION. *Schuyler G. Kohl, M.D. and Glenn Casey, B.S.* 523

ALCOHOLIC PANCREATITIS. *Henri Sarles, M.D., Catherine Figarella, and Osvaldo Tiscornia, M.D.* 540

SMALL BOWEL STRUCTURE AND FUNCTION IN PANCREATIC STEATORRHEA. *Simmy Bank, M.B., Ch.B.* 552

TECHNIQUES AND DOSIMETRY FOR INFLATABLE MINIATURIZED AFTERLOADING IN CANCER OF THE CERVIX. *Norman Simon, M.D. and Sidney M. Silverstone, M.D.* 565

COXSACKIE HEPATITIS IN AN ADULT, WITH ULTRASTRUCTURAL DEMONSTRATION OF THE VIRUS. *Gregory R. Gregor, M.D., Stephen A. Geller, M.D., George F. Walker, B.A., and B. A. Campomanes, M.D.* 575

ILEOCOLIC INTUSSUSCEPTION PRESENTING AS A LEFT UPPER QUADRANT MASS, MASQUERADING AS A PANCREATIC PSEUDOCYST. *Ernest J. Mencer, M.D., Chun Loh, M.D., and A. James McElhinney, M.D.* 581

ENDOMETRIAL CARCINOMA IN TURNER'S SYNDROME FOLLOWING PROLONGED TREATMENT WITH DIETHYLSTILBESTROL. *David K. Sirota, M.D. and Stanley C. Marinoff, M.D.* 586

MELANOCYTES IN MUSCLES OF MASTICATION. *Frederick G. Zak, M.D. and William Lawson, M.D.* 591

LATERAL SUBCUTANEOUS INTERNAL SPHINCTEROTOMY FOR ANAL FISSURE. *Changyul Oh, M.D.* 596

RADIOLOGIC NOTES. *Claude Bloch, M.D. and Harvey M. Peck, M.D. Coeditors*

DISPLACEMENT AND REORIENTATION OF A STAGHORN CALCULUS. *By Alex Berenstein, M.D.* 602

URETEROCELE PROLAPSED THROUGH THE FEMALE URETHRA. *By Alex Berenstein, M.D.* 608

OPHTHALMOLOGIC NOTE. *Keith M. Zinn, M.D., Editor*

OCCULT OCULAR MELANOMA. *By Keith M. Zinn, M.D. and Mark Goldfarb, M.D.* 615

THE STUDENT'S CORNER. *Jeffrey Buckner, B.S., Editor*

MEDICAL EDUCATION ABROAD. *By Judi Ehrenfeld, B.A., M.A.* 620

LETTER TO THE EDITOR.

PATHOLOGIST'S DIAGNOSIS/SURGEON'S DILEMMA. *Bernard Bruce Wetchler, M.D.* 622

INDEX TO VOLUME 42 i

TABLE OF CONTENTS OF VOLUME 42 .... C1

SUPPLEMENTUM

A STUDY OF THE ADRENOCORTICAL DISORDERS RELATED TO THE BIOSYNTHESIS AND REGULATION OF STEROID HORMONES AND THEIR COMPUTER SIMULATION. *Dinesh C. Sharma, D.Sc., Ph.D., J. Lester Gabrilove, M.D., and Anne D. Borror* S1

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Colonoscopy: A Clinical View*

JEROME D. WAYE, M.D.

Within the past decade the entire field of colonoscopy has developed and now permits the physician to extend his field of vision from the distal-most 10 inches of the rectum and sigmoid to the entire large intestine, including the descending colon, transverse colon, ascending colon, and cecum. Every centimeter of the mucosal surface now can be completely examined, prodded, photographed, and biopsied by the noninvasive procedure of colonoscopy. Turell (1) presented the first paper describing a fiberoptic colonoscope in 1963 and Overholt (2, 3) developed the technique in the United States. Other workers (4) tied a direct-viewing upper intestinal endoscope onto an orally ingested, rectally extruded plastic tube. The instrument was pulled into the colon by this "tube technique" which involved several days of preparation (5–7). Developments have been rapid, and instrumentation has kept abreast of manipulative techniques so that modern colonoscopes are introduced into the rectum and guided to the desired depth under direct vision with all guidance controls external to the patient.

Benefits to the patient are manifest. Colonoscopy, with the ability to biopsy any lesions present in the lumen or on the mucosal surface of the bowel, permits precise histologic diagnosis of pathologic conditions. Lesions seen on x-ray can be quickly evaluated, artifacts present on x-ray can be readily ruled out, sources of bleeding can be located, and surgeons can utilize the knowledge gained to plan operative procedures. Colonoscopic polypectomy has now become an accepted, well-defined procedure for the removal of colonic polyps; the wire snare and cautery technique has almost completely replaced the need for open surgical operations to resect colonic polyps. Because of the knowledge and information that can be gained concerning disease processes, colonoscopy should be available in many community hospitals as well as in larger teaching centers.

There have been few reviews concerning the use of the colonoscope (8–12) in general medical journals. Many articles have appeared in gastroenterology specialty journals (13–18), but these do not receive wide dissemination among practicing physicians. This article is an in-depth review based on a personal experience of several thousand colonoscopies, as well as a considerable volume of direct communications with colonoscopic experts throughout the world.

It is important to realize that problems related to patient tolerance, patient acceptance, safety and complications are inherent in the technique of colonoscopy. The technique involves propelling a long tube deep into the body by the coordinated multi-sequence functions of twisting, pulling and pushing on the shaft of the instrument while simultaneously insufflating air or water, and rotat-

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From the Department of Medicine, Division of Gastroenterology, The Mount Sinai Hospital, and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

* Figures in italics denote color photographs. All color for this article is on page 19.

ing dials to move the tip in the desired direction. One must be aware not only of indications and contraindications, but of the economics involved in the procedure as well. These points will be covered in this article.

Fiberoptic Systems

Tiny glass fibers are responsible for the visual characteristics and flexibility of the fiberoptic endoscopes. Each glass fiber is 10–20 micra in diameter and several thousand are grouped together to form a bundle of fibers. A spot of light entering one end of an individual glass fiber "bounces" along the walls of that fiber and emerges at the opposite end. The light which emerges is 95 percent as bright as the light which enters, for there is scarcely any diminution in brightness of vision during the passage of light along the course of a fiber bundle. Scattering of light from one fiber to its adjacent neighbor is prevented by coating each glass fiber by a micro-thin layer of glass of a different refractive index. Neither lenses nor prisms are necessary for light transmission, but a lens system is used to focus the subject onto the distal end of the glass bundles, and another lens system is used to magnify the image obtained on the proximal end. The visual fiber bundles are spatially oriented so that an object viewed upright at the distal end is projected upright on the image lens on the proximal portion of the instrument with preservation of right-left discrimination. The bundles that transmit both light and image are referred to as "coherent" bundles, whereas "incoherent" bundles have no specific alignment and only transmit light (19, 20). The thousands of glass fibers are fused into one bundle proximally and distally, and are free throughout most of their length, giving rise to the extreme flexibility of the instruments and to the capability of "bending" light around corners, achieving image transmission even though the fibers are tied in a knot. Each fiber transmits a fraction of the image viewed, and it is re-integrated as a mosaic of multiple spots of light at the instrument eyepiece.

Light used for endoscopic illumination of body cavities is generated in a separate light source outside the patient, and is transmitted into the intestinal lumen by a separate incoherent fiberoptic bundle. The light source may be a xenon or mercury arc or a halogen lamp, permitting brilliant illumination without dependence on a "hot" incandescent bulb at the tip of the instrument. The "cool" method of illumination completely circumvents the problem of a burn of the intestinal mucosa caused by the heat generated when the older type of endoscopic instrument was used. The degree of illumination achieved with the fiberoptic instruments permits both still and motion color photography within the gastrointestinal tract. The external light sources vary in size from a portable table model to a large floor model console.

Instrumentation

American Cystoscope Makers, Inc. (ACMI) built the first prototype fiberoptic colonoscope in 1963 (1), but the first instruments with deflective tips were developed in Japan in 1966 (21, 22), and are manufactured by the Olympus

Corporation of America. The original instruments were approximately 85 cm in length, but the manufacture of these has been discontinued. Two lengths of colonoscope are currently in use; the "medium," 105–110 cm, can routinely reach the mid-transverse colon, while the "long" instrument, 165–185 cm, may reach the cecal tip or enter the ileocecal valve. The medium-length instruments are easier to use and are the most popular at the present time. The distal several centimeters of all instruments can be deflected through any range of right-left, and up-down motions by controls on the proximal end. The ACMI instrument is manipulated with a stick lever (Fig. 1), while the Olympus instrument is controlled with a dial mechanism (Fig. 2). In addition to the separate fiberoptic viewing and illumination bundles, the colonoscope contains a separate water channel, the tip of which is constructed so that a cleansing spray is directed across the viewing lens at the tip of the instrument. This spray is used to wash accumulated mucus and stool from the lens surface during the examination. Adequate visualization of the intestinal lumen is accomplished by insufflation of air, either through the water channel or via a separate channel. Excess air, mucus, and liquid fecal material can be withdrawn from the colon during the examination through a separate small suction channel. Only liquid material can be removed through this small channel which varies in size from 3 to 4 mm in diameter, depending on the instrument used.

The Olympus instruments are 14 mm in diameter and make use of the suction channel to introduce various forceps, wire snares (Fig. 3), and cytology brushes deep into the colon. A mechanism is built into the tip of the fiberscope to elevate the biopsy forceps by 15 degrees from the horizontal position. ACMI has introduced a colonoscope, 15.8 mm in diameter, with two separate channels (the largest 4 mm in diameter) so that adequate suction can be maintained while a for-

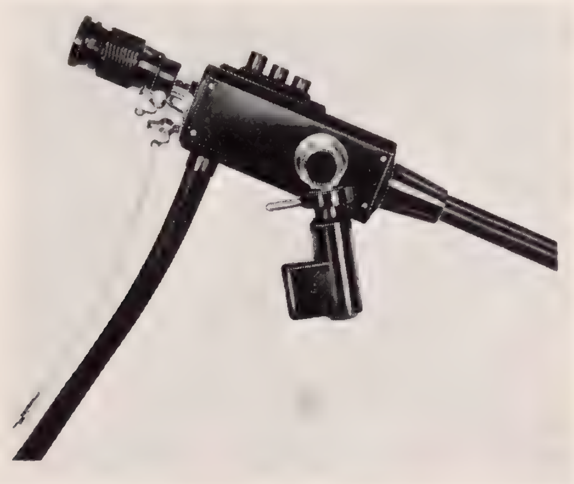


Fig. 1. Head of the ACMI colonoscope with stick-lever control mechanism. Depression of buttons on top provide suction and air. The small plastic tube permits instillation of water for cleansing of the distal lens.

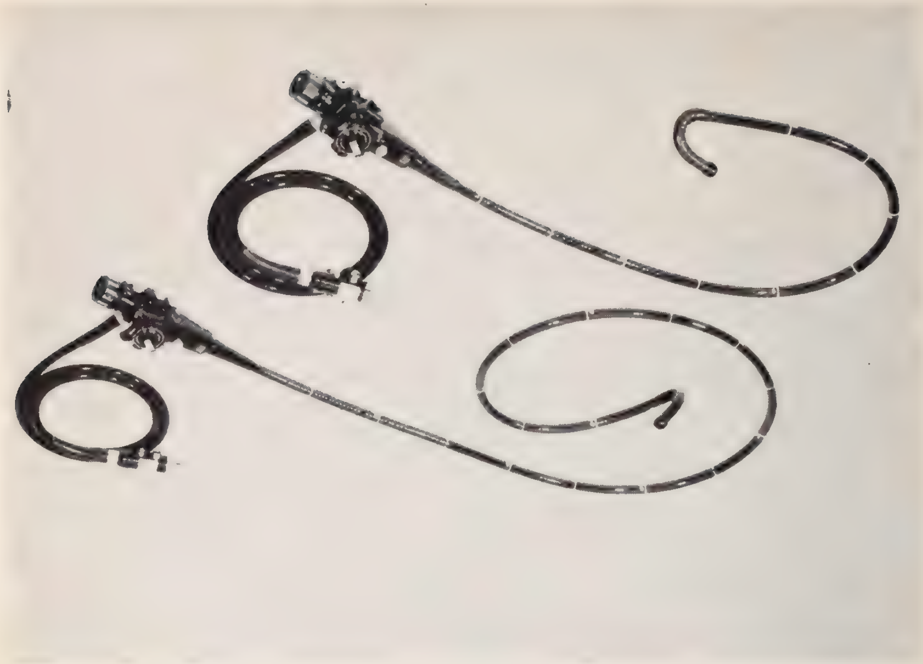


Fig. 2. Two models of Olympus colonoscopes. The MB2 is 112 cm in length while the LB2 is 187 cm. Tip deflection is controlled by dials on the head of the instrument and air/water/suction are integral parts of the system.

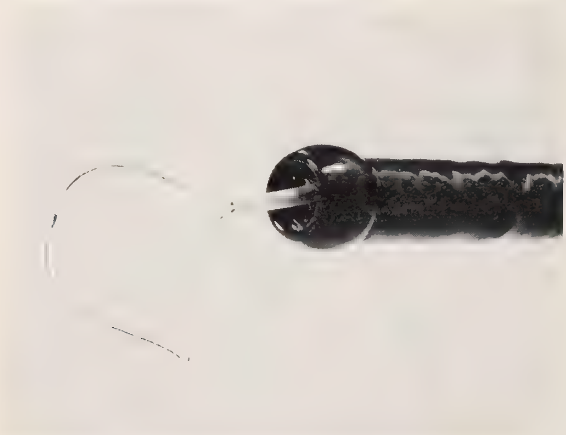


Fig. 3. Wire snare extended from tip of Olympus colonoscope; 15° deflection of the polyethylene catheter is obtained by controllable mechanism.

ceps is in one channel or so that two different biopsy and/or snare instruments may be introduced at the same time into the colon (Fig. 4). Machida Endoscope Co., Ltd., of Japan is the only other company manufacturing colonoscopes for use in the United States. On all instruments, the use of water, air and suction are

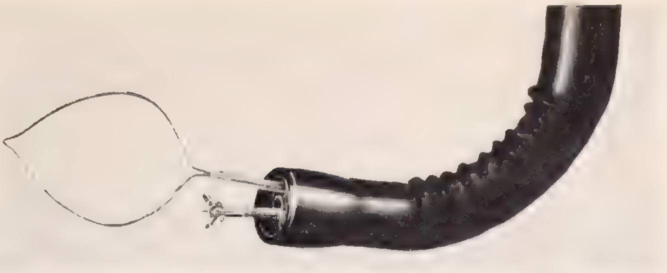


FIG. 4. Double channel ACMI colonoscope with forceps and snare extended simultaneously.

activated by controls on the proximal end. Because of the increasing use of colonoscopes for removal of polyps, all are now being manufactured with grounding devices and ability to insufflate CO_2.

Instrument Accessories

Biopsy forceps, placed through the suction port of the instrument, are necessarily of small caliber, and the amount of tissue which can be obtained is limited. When open, the span of the jaws of the biopsy forceps is approximately 7 to 8 mm. Both ACMI and Machida companies make a biopsy forceps with a center spike which aids in fixing the forceps at the site desired. The jaws of the ACMI forceps are longer than the Olympus round "butterball" forceps and can provide a larger specimen. At times the longer, inflexible head of the larger forceps is difficult to pass through the instrument when several curves are present and the tip is acutely flexed. Cytology brushes are easily passed and adequate specimens can be obtained for cytologic evaluation. Techniques have been developed to attach a "water pick" to a long Teflon® tubing permitting a high velocity pulsatile flow of saline into the colon for exfoliative cytology (23–24). Several companies are manufacturing snares for removal of colonic polyps which can be used with both the medium and long instruments. A rapidly proliferating variety of electrocoagulation instruments are available. Various methods are being developed for "stiffening" the instruments if that property is desired for achieving passage around various colonic bends. A wire can be placed into the biopsy channel for internal stiffening (25, 26) or a plastic sheath can be slid along the outside of the shaft up into the sigmoid colon for external stiffening (27). The uses for these will be discussed later. Separate fiberoptic teaching attachments can be purchased permitting an observer to watch the intraluminal progress of the instrument along with the examiner. Small portable television transmitters are becoming available that will project the endoscopic image onto a color television screen for an unlimited number of observers to view simultaneously. Still photography through the instruments is accomplished with easily attached bayonet-type fittings. The use of single-lens reflex cameras allows complete visualization of the pictorial field. Movie cameras are also easily attached and adequate movies can be taken either with super-8 or 16 mm color film. The state of endoscopic photography has progressed to the point that the examiner need only mount the camera on the instrument and press the shutter-release button. The Olympus light sources contain an electronic shutter that integrates light intensity and distance from the subject.

Indications for Colonoscopy

The major factor which prompts most colonoscopic examinations is an abnormal barium enema radiographic examination. A lesion visualized on x-ray can be biopsied through the colonoscope; and, while providing an exact histologic diagnosis, intracolonic photographic records can be obtained for future references. Persistent symptoms such as colonic bleeding or diarrhea with a normal barium enema are also indications for colonoscopy because small lesions such as carcinoma, polyps, nonspecific ulcers of the colon, telangiectasia, and inflammatory bowel disease may all be present and not demonstrated on the x-ray. Known cases of inflammatory bowel disease may have the extent of inflammation and the type of disease more precisely characterized by direct vision and mucosal biopsy. Knowing the exact extent of disease may aid the surgeon in his preoperative planning in inflammatory bowel disease. Colostomies or ileostomies can be easily examined; and differential diagnosis between "stomal dysfunction" and recurrent inflammatory disease is possible. A precise radiographic differential diagnosis between carcinoma and diverticulitis is ofttimes difficult when complete obstruction to the retrograde flow of barium is present in the sigmoid colon but they can be definitively differentiated with the endoscope.

Among the therapeutic uses for endoscopy are the removal of polyps, both sessile and pedunculated, the removal of foreign bodies, and reduction of volvuli of the colon.

Specific contraindications for colonoscopy are few indeed. In general, if cathartics are contraindicated, then colonoscopy should not be performed; this includes peritonitis, perforation of the colon and various types of acute colitis. Since adequate cleansing of the colon is of prime importance to permit adequate visualization through the endoscope, patients must be able to be prepared both with cathartics and enemas. Colonoscopy may be safely performed if this vigorous preparation can be tolerated by the patient.

There is no advantage in performing colonoscopy in acute ulcerative colitis when the diagnosis can be made by history and sigmoidoscopic examination. The patient who has massive rectal bleeding usually cannot be adequately prepared, and colonoscopy is unrewarding. With the newer double-channel instruments, it may be possible to wash with water and to suction blood and clots simultaneously, but more experience is necessary. The uncooperative patient may present a relative contraindication to the procedure, if that patient cannot be induced to relax.

Preparation of the Patient

The ideal colon preparation for endoscopy is a bowel completely devoid of solid fecal material with no semisolid stool clinging to the bowel surfaces.

The small suction/biopsy channel of the fiberoptic instruments becomes rapidly plugged and ineffective if any solid stool is present and is suctioned into that channel. If vegetable matter or fecal material larger than 5 mm is sucked into the biopsy port, it may not only become stuck onto that port, but may also occlude the light bundle or the visual lens, rendering further intubation impossible. Avoidance of solid food, cathartic inducement of diarrhea, and mechanical cleansing by enemas provide a reasonably clean bowel in most instances. The fine spray of water used to clean the lens is completely ineffective in dislodging a piece of fecal matter in which the instrument has become impacted or which has been firmly fixed to the endoscope by suction.

In almost every instance the ideal preparation can be achieved by maintaining the patient on a liquid diet for 24 to 48 hours, administering 1–2 ounces of castor oil the night prior to examination, and giving 2 tap-water enemas on the day of the procedure. The last enema should be given at least 2 hours prior to the procedure so that adequate evacuation of enema fluid may occur and "spasm" induced by the enema can subside. Purgative enemas (oxyphenisatin (12) or bisacodyl (28)) and saline (28) have been used in place of tap-water enemas, but I have not had occasion to use these preparations. Cathartics other than (9, 14, 28, 29, 30) castor oil may also be effectively used to cleanse the bowel and the desired result should be a liquid diarrhea, no matter which of the cathartic agents are used. Cathartics may be avoided altogether if no solid food is given for several days (14) and the liquid diet is supplemented with a nutrient solution (Vivonex®) (31).

In spite of vigorous cleansing, patients with diverticulosis frequently retain inspissated stool within diverticuli which may dislodge during the examination and cause annoying problems. In patients with inflammatory bowel disease with active diarrhea a cathartic is not necessary; however, the patient should be on a liquid diet and enemas should be administered. If the patient has inflammatory bowel disease but is not having more than 3 bowel movements per day, a mild saline cathartic should be given, as well as a liquid diet and enemas.

Every patient should be interviewed before the endoscopic procedure and the nature of the examination explained and reassurance extended. The apprehension experienced by patients can be diminished by informing them of the necessity of the examination and the goals desired. The patient must be made aware that the liquid diet is a part of the procedure, as are the purgation and enemas. Many patients request that they be "asleep" during colonoscopy, but can be easily convinced to accept the routine sedation if proper reassurance is given.

Colonoscopic Medication

The degree of discomfort varies from patient to patient and many find colonoscopy, without any medication, somewhat less traumatic than either a barium enema examination or a routine rigid sigmoidoscopy. Two parts of the colonoscopic examination may be uncomfortable for the patients. Some patients experience considerable discomfort when the colon is distended by air insufflation. Since the colonoscope is a solid instrument, the intracolonic pressure does not equilibrate with room air, such as occurs during sigmoidoscopy. Adequate distension of the colon is an absolute necessity for a successful examination; if air is not injected the colon is collapsed and the walls coapted so that no lumen is visible. Overdistension of the bowel with air is easily remedied by withdrawal of air via the suction apparatus. The awake patient will complain that he has considerable discomfort or the nurse/assistant will inform the examiner of marked abdominal distension. Traction on the colonic mesentery is another cause of considerable patient discomfort. As the instrument assumes the configuration of the sigmoid colon, and bends into an "N" pattern (Fig. 5), further introduction into the rectum may only cause widening of the first loop with a large inverted "U" pattern. This occurs when the tip of the instrument is flexed at the junction of the acute angle between the sigmoid and descending colon, and the tip may not advance even though more of the instrument is being pushed into the rectum. The enlarging inverted "U" loop may stretch the sigmoid to the level of the diaphragm, causing painful internal traction on the root of the sigmoid mesocolon. Much of the discomfort caused by this mechanical pulling during endoscopy can be relieved by appropriate medication. The endoscopist should be guided by the patient; if discomfort occurs, maneuvers aimed at decreasing the amount of air distension or decreasing traction on the mesentery should be employed. Because of the desirability of having the patient inform the physician of any discomfort, examination under general anesthesia is to be avoided if at all possible. In children, colonoscopy and even polypectomy can be performed with merely heavy sedation; however, procedures may be more easily accomplished under general anesthesia (18). We have only recently begun using a combination of meperidine and diazepam for all colonoscopic procedures, but some endoscopists do not use any medication. It is my distinct impression that patients tolerate colonoscopy much better with some degree of analgesia than without any medication. Both with and without medication, colonoscopy is tolerated better by the older rather than the younger patient.

To facilitate the direct intravenous injection of analgesic agents, I have employed the use of a small butterfly or scalp-vein needle with direct intravenous

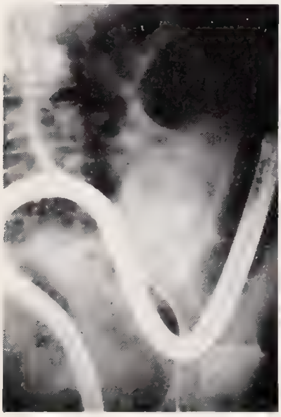


Fig. 5. "N" configuration of the instrument. Although the tip of the instrument is in the mid descending colon, further introduction into the rectum will only cause an enlargement of the inverted "U" loop with subsequent discomfort for the patient.

injections of 25 to 50 mg of meperidine and 5 to 15 mg of diazepam. Older patients usually require a smaller dose of medication than younger patients. To avoid precipitation of the two agents, and to avoid the phlebitis which frequently occurs following intravenous use of diazepam, 1 or 2 cc of saline is injected through the scalp-vein needle after meperidine and several cc are used to flush the tubing and vein after diazepam. The syringe with saline is left connected to the scalp-vein needle and taped to the forearm so that further medication may be injected as necessary during the procedure. A nitrous oxide-oxygen demand type inhalation anesthesia has been described (32) as being useful during the colonoscopic procedure, as have various antispasmodic drugs (29). With the combination of medication used at The Mount Sinai Hospital, patients are usually sedated during the procedure but do respond when discomfort arises.

Nervous innervations stimulated by manipulation of the mesentery (by traction) may, combined with the intravenous analgesic medication, cause a typical vagal response of hypotension, diaphoresis and emesis. Partial withdrawal of the instrument or termination of the procedure will give rapid regression of all symptomatology. If the ileocecal valve is incompetent or if the patient becomes overly distended and air distends the small bowel, the patient may retch and vomit. Suction of gas from the intestine or decreasing traction on the mesentery may both help to alleviate the emetic response.

General anesthesia plays no role in routine colonoscopy (14, 33, 34) because the level of discomfort experienced during endoscopy is not great and the risks of anesthesia outweigh its benefits. Whatever discomfort occurs assists the examiner to decide whether he can continue to advance or should withdraw the instrument. In several thousand examinations I have used general anesthesia once, during polypectomy in an 18-month child.

Colonoscopy under general anesthesia during laparotomy, to locate a site of previous polypectomy for the surgeon, or to pinpoint a specific site of bleeding, may be of great benefit. During laparotomy, the abdominal surgeon may assist in guiding the instrument around the various flexures of the colon (35), thereby facilitating its rapid passage. The amount of air necessary for bowel insufflation causes hyperdistension of the colon when the abdominal wall is opened. It may not be possible to evacuate all the air through the colonoscope prior to its removal and the surgeon then must contend with a greatly distended large bowel, increasing the difficulty of the surgical procedure.

Anticholinergic drugs have a tendency to create an atonic colon, which may become overdistended with air. I have not found the use of anticholinergic agents helpful in passage of the colonoscope, even in cases of diverticulosis and diverticulitis with spasm.

Technique of Examination

A few authors have addressed the general technique of colonoscopy (16, 36, 37); the method I use is detailed below.

The patient is placed on a stretcher or examining table in the left lateral recumbent position. This position is used throughout the entire procedure. The examiner stands behind the patient. The hips are flexed at 90 degrees to the body so that the anus is exposed and manipulations can be performed close to the anus without interference from the thighs. The knee-chest position offers no advantage during the passage of the colonoscope and may even make the examination somewhat more difficult while intubating the sigmoid colon. The room in which the examination is performed is non-sterile, and the examination is usually "clean" without fecal soilage. In our Endoscopy Unit, the endoscopist usually wears "street clothes" during the examination, and does not change into O.R. scrub suits. The patient is reassured that the procedure will not be severely uncomfortable and a butterfly needle is placed into a vein. After the medications are injected the patient usually feels somewhat drowsy but is awake during the procedure. A rectal examination is performed for two purposes. The first is to dilate the rectal sphincter and determine whether a stricture exists in the area of the anus. The second purpose is to ascertain whether the rectum contains solid stool material. If solid stool is present in the rectal ampulla, the procedure should be discontinued and further cleansing is required. An experienced endoscopist may be able to intubate an unclean colon, but such examinations are usually not satisfactory. With the patient in the left lateral position, the well-lubricated instrument is inserted approximately 2 inches through the anal canal. Mucus usually collects at the tip as the instrument passes through the rectal canal and the lens should be washed with water (by the appropriate proximal control) after it has been introduced. Air is then insufflated, and a combination of turning the proximal control dials, as well as rotation (application of torque) of the shaft of the instrument, is used to locate the lumen of the bowel. In the rectum and sigmoid, whenever a semilunar fold is present stretching across the field it is known that the lumen continues behind that fold. The instrument is advanced up to the fold and the tip of the instrument is bent into the direction of the fold while the shaft of the instrument is rotated (torqued) into the direction of the fold. Visualization of the lumen is accomplished by a combination of deflecting the tip of the instrument upward or downward and twisting the shaft of the instrument in a clockwise or counterclockwise direction. The Olympus colonoscope permits the entire examination to be performed by one operator. No assistance is necessary for passage of the instrument, since the dials are small enough to be manipulated with the thumb of the left hand which also holds the head of the instrument, while the right hand holds the shaft of the colonoscope near the rectum and rotates it while advancing or withdrawing it. The ACMI colonoscope has a "stick" mechanism for control of tip deflection, with up-down motion provided by pushing or pulling the lever while rotation moves the tip in a right-left direction. Few endoscopists can manage to grasp the head of the instrument and manipulate the stick lever with one hand, and use of the ACMI colonoscope usually requires the examiner's two hands on the head of the instrument; the left hand to hold the head, the right to operate the polydirectional lever. An assistant is usually required to advance, withdraw and rotate the instrument. A neck brace has been manufactured by ACMI to hold the head of the instrument, thus freeing the left hand for manipulation of the shaft of the colonoscope. This brace is a curved piece of metal which fits around the neck and utilizes a chestplate on which to rest the instrument. An adapter is available to permit thumb control of the ACMI up-down tip deflection, but requires a large handspan for its use. An assistant/observer may watch the intralumenal progress of the instrument through a "teaching" attachment, a separate fiberoptic instrument that is placed on the operator's eyepiece. Only slight diminution in visual acuity and brightness is seen during the use of these sidearm attachments.

After 20 to 30 cm of instrument have been inserted, forward motion of the instrument may become difficult. Fluoroscopy will demonstrate that the colonoscope enters the rectum and, after progressing straight for 10 cm, forms a gentle semicircular curve to the left with the tip deflected downward to the left lower quadrant. The acute angle formed in the left lower quadrant at the junction of the sigmoid and descending colon is frequently the most difficult flexure for the endoscopist to pass. With the tip pointed into the left pelvis (Fig. 6) further advancement of the instrument into the rectum will not propel the tip around the acute sigmoid-descending colon angle, but will only serve to stretch the sigmoid into a huge inverted "U" pattern. When this occurs there are two techniques that may be used to reduce the acute angle at the sigmoid-descending colon junction.

The first of these techniques is widely known as the formation of an "alpha-loop" (16, 18, 38). The patient is rolled into a supine position with the right leg flexed. The examiner grasps the shaft of the instrument near the rectum and rotates it 180 degrees in a counterclockwise direction so that the rounded curve

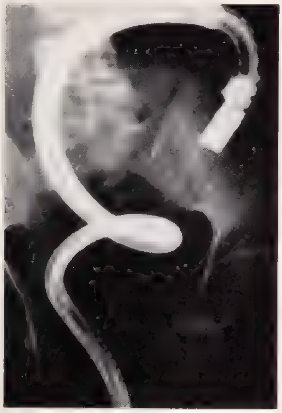


FIG. 6.

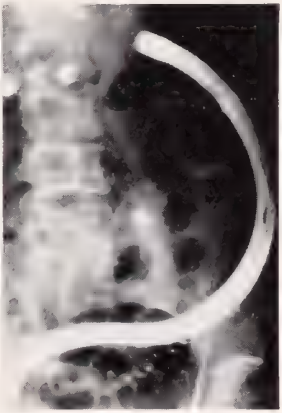


FIG. 7.

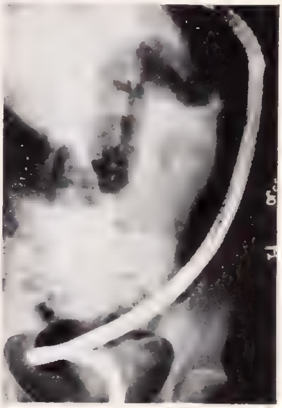


FIG. 8.

FIG. 6. The tip of the instrument is pointed downward into the left lower quadrant at the junction of the sigmoid and descending colon. An extra coil is in the rectum. Further pushing will only increase the coil and bow the sigmoid mesocolon.

FIG. 7. A smooth gentle curve around the sigmoid. The tip of the instrument is in the upper descending colon. Straightening the tip will permit the instrument to reach the splenic flexure.

FIG. 8. The tip of the instrument is at the splenic flexure. The loop in the sigmoid is small, and may not interfere with further passage of the instrument. By hooking the tip and withdrawal of the instrument from the rectum (jiggle), the sigmoid loop can be straightened.

of the colonoscope with the tip in the left lower quadrant has shifted and the curve now points toward the right, with the tip of the instrument in the right lower quadrant. This maneuver may be manually assisted by placing a hand in the left lower quadrant and actually pushing the instrument across the midline with the abdominal palpating hand. The sigmoid mesocolon has now been displaced and stretched from its usual location in the left lower quadrant to the right lower quadrant. The sigmoid is also stretched and the instrument is then advanced through the sigmoid, crossing from the right lower quadrant across the midline of the abdomen and up the descending colon. The acute angle has been converted to a gentle sweep extending across the midline. Fluoroscopy is usually required to ascertain if the proper configuration is achieved, and if one fluoroscopes the patient with the instrument in this position, it resembles the shape of the Greek letter "alpha." This maneuver is performed with a minimal amount of discomfort for the patient.

The technique that I use to overcome the problem of the acute angle at the descending colon is to straighten out the sigmoid curvature by "pleating" the colon upon the instrument. This is accomplished by a combination of flexing the tip acutely ("hooking") at whatever point forward progress is impeded, and "jiggling" the well-lubricated instrument with an in-and-out motion at the rectum. During each of these jiggling maneuvers, the instrument is withdrawn slightly more than it is advanced, thereby slowly straightening out the loop in the sigmoid colon. The bowel will pleat upon the instrument in an accordian-type pattern and the inverted "U" configuration of the instrument becomes reduced until the tip of the instrument assumes a straight line from the rectum to the descending colon (Fig. 7). At this point, the tip of the instrument is straightened and the instrument can be easily advanced into the descending colon.

Once the tip of the instrument is located in the descending colon, further advancement of the instrument may tend to reestablish the original sigmoid loop (as shown in Figure 5) and further introduction of the instrument in the rectum may serve to increase the loop in the sigmoid without permitting the tip to advance deeper into the colon. I keep the loop from re-forming by continually flexing the tip of the scope acutely and "jiggling" the instrument with gradual withdrawal after advancing it several centimeters. Various "stiffener" devices can be used to prevent the sigmoid angulation from recurring once the sigmoid has been traversed. An external plastic sheath (30–40 cm long) may be used which is slid over the instrument shaft prior to its original insertion into the rectum. Once the instrument has reached the descending colon either with the jiggling technique to straighten the instrument, or with the alpha-maneuver, the stiffener device is slid forward from its "holding" position near the head of the shaft. Use of this stiffening device is recommended only under fluoroscopic control to insure the proper alignment of the colonoscope. Appropriate techniques have been developed to permit the advancement of the stiffener fluoroscopically simultaneously with the untwisting of the alpha-loop, but it cannot be inserted while the alpha-loop is present, nor can it be used as a "ram" to straighten out the instrument or the sigmoid. Since the stiffening device is fairly rigid, it should not be passed over the instrument unless the shaft of the instrument is straight lest the device rupture the scope or perforate the bowel wall. The external splint is used only with the long colonoscopes since the length of the device, when slid over the shaft of the shorter scope, leaves too little of the instrument free for manipulation in the sigmoid. The purpose of the stiffener is to maintain straightness of the sigmoid colon so that the tip of the instrument may be passed into the transverse and ascending colon without the tendency for reforming the sigmoid curvatures. An internal stiffener is available, a wire device with a coil spring which can be tightened from outside the colon, so that once the wire is placed throughout the entire length of the instrument or any portion thereof, tightening the device causes it and consequently the instrument to become extremely stiff. This has been associated with rupture of the biopsy-suction channel of the instrument, since this device creates great internal strain on the endoscope unless the instrument is relatively straight or has gentle curves and not acute tight spirals. I do not use stiffening devices for passage of the colonoscope because I do not use fluoroscopy during colonoscopy.

Use of Fluoroscopy during Colonoscopy

Several articles have pointed out the "absolute necessity" for fluoroscopy (12, 18) to assist in passage of the instrument, as well as in locating the tip of the instrument (31). During my first 25 colonoscopies, fluoroscopy was used in every case. Because the fluoroscopic unit was not easily accessible to the endoscopic unit, attempts were soon made to develop a technique which would permit passage of the instrument without the use of fluoroscopy. The technique that has been developed is quite feasible and I have not used fluoroscopy for the last 3000 colonoscopies. Other endoscopists use fluoroscopy sparingly or not at all (9, 39, 40, 41). The technique of "non-fluoroscopic colonoscopy" is quite effective and residents and visiting physicians are easily trained in the technique of passage without reliance on fluoroscopic guidance. If a fluoroscopy unit is easily available to the endoscopist, it may be helpful to use it for locating the tip of the instrument. One does not need fluoroscopy to know that an internal loop is being formed in the sigmoid or elsewhere, since one must assume a loop is forming whenever the instrument is pushed into the rectum and there is either no forward motion of the tip along the mucosa or the tip moves forward a shorter distance than the amount of shaft introduced into the rectum. After "hooking" and "jiggling," even without fluoroscopy, the examiner knows the colonoscope is straight when one achieves a one-to-one relationship between the amount of shaft advanced into the rectum and the distance travelled by the tip of the instrument across the mucosa. Once the tip is in the descending colon, and more scope is being advanced, frequently there is a tendency for relooping to occur. The formation of a loop will be evident to the non-fluoroscoping endoscopist whenever one loses the one-to-one ratio of the forward motion of instrument tip to the amount of shaft introduced into the rectum. When the tip continues to move forward even though at a slower rate than the instrument is being advanced rectally, a loop is being formed, but there is no need to reduce the loop unless it becomes uncomfortable for the patient, or the instrument is advanced to its limit at the rectum and further forward progress is desired (Figs. 8 and 9). "Paradoxical motion" of the instrument is another indication of a loop-formation. As more of the shaft is introduced into the rectum the tip of the instrument may actually move in a retrograde fashion along the mucosa, again due to the formation of a loop. The explanation of this is: as an "inverted U" is formed and begins to arise out of the pelvis, the force vector is shifted from advancing the tip forward to the apex of the inverted "U," and as the apex of the "U" rises higher because the scope is being pushed into the rectum, the other limb of the "U" loop is dragged upward, causing the tip to be pulled several centimeters in retrograde fashion. This can only be rectified by jiggling the instrument from the rectum to remove the excess loop. Frequently, as the loop is being straightened, with the instrument being jiggled, the tip will spring forward through the colonic lumen by several centimeters, further indicating that the loop is being withdrawn and straightened. Knowledge of the problems of looping, hooking, coiling and "paradoxical motion" will tell the colonoscopist as much about the internal configuration of the instrument as he can derive from fluoroscopy. I have been told that fluoroscopy assists in ascertaining the location of the lumen when it is difficult to locate. There is no doubt that this is a very real problem, and for the neophyte endoscopist, or the non-endoscopist, it is difficult to imagine that the instrument may be in the mid-descending colon, with the tip bent acutely, and one can only see wall of bowel without being able to visualize the lumen, but this happens frequently. I have found that fluoroscopy is not necessary to establish the direction of the lumen, but if it is not used, one must pay attention to minute details, so that the direction of lumen is always known before the instrument is advanced. One of the techniques that has been used by colonosco-

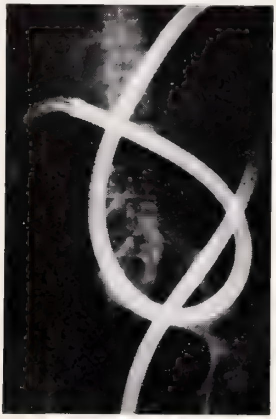


FIG. 9.

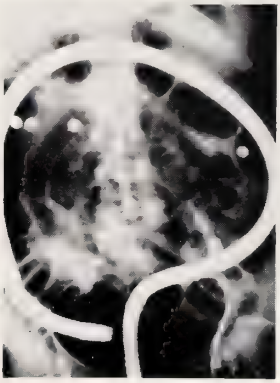


FIG. 10.

FIG. 9. The sigmoid is straight and the tip of the instrument is in the ascending colon. A loop is in the transverse colon. Further introduction will only serve to increase the transverse colon loop. With the tip flexed, withdrawing the instrument from the rectum will reduce the loop.

FIG. 10. All looping has been reduced, and the tip is in the cecum.

pists is "slide-by" (42). This implies advancing the tip of the instrument along the mucosal wall without seeing the lumen. This must be done gently and forward motion of the instrument must be stopped once resistance is encountered or blanching of vasculature is seen lest a perforation occur. I feel that it is unsafe to advance the instrument unless the lumen is seen or one knows exactly in which direction it is located. A tubular view can usually be achieved if the instrument is jiggled and gradually withdrawn. Withdrawal of the instrument always permits one to revisualize the lumen. Many colonoscopists, having advanced the scope to a certain level, are extremely reluctant to withdraw the instrument from the rectum for fear that they will retract from their position in the colon. This should not be of great concern, for once the instrument has been passed to a certain depth, it can always be reinserted to that level. Withdrawal of the instrument, and straightening it while doing so, is the most important technique to be learned by the colonoscopist. It is my opinion that the right hand on the shaft of the instrument is more important than the hand manipulating the control mechanism at the proximal end. The right hand guides the scope around curvatures by torquing to the right and left, while using the maneuvers of advancing, withdrawing and jiggling. By straightening the bowel into a gentle loop with the endoscope, the tip may be in the cecum while only 70 to 75 cm of instrument is within the colon (Fig. 10).

A non-fluoroscopic technique that can be used to identify the direction of the lumen is to direct attention to the areas of reflected light from the convolutions and ridges formed by the mucosa stretched over the circular muscle of the colon. The use of "highlights" is extremely important in colonoscopy and I shall describe their significance. The colon is tubular, and the mucosa is folded and convoluted upon itself. As the lumen of the bowel becomes distended with air during colonoscopy, the mucosa becomes stretched and thinned-out against the submucosa. Because the circular muscle of the colon is not completely smooth, the flattened-out mucosa assumes a very slight "corrugated" appearance in the distended colon. Reflections of light from these small circumferential ridges are usually reflected in a curved arc, rather than straight lines. Since these ridges are circumferential, the reflected light along an arc, however short that curved reflection may be, should be a clue to the examiner that the lumen is toward the concavity of the arc, and if the controls direct the tip away from the curvature of the arc, it will be directed toward the lumen. Fluoroscopy will also enable one to point the tip in the proper direction, but it is not necessary.

It should be noted that excess use of fluoroscopy during colonoscopy may cause radiation damage to the fiberoptic bundles of the instrument, with "yellowing" and damage. Colonoscopy without fluoroscopic control has been likened to examination of the chest without a stethoscope (43), but many endoscopic units are small, the availability of fluoroscopic equipment is limited, and the expense prohibitive. I feel that colonoscopy can safely be performed in any office or examining room without the need for fluoroscopy. If a fluoroscopic unit is conveniently available, it should be used to assist the fledgling colonoscopist to identify segments of the colon and landmarks which he may later accept as "fixed areas" and for which later he may not need to rely on fluoroscopy to ascertain the location of the tip of the instrument. If a colonoscopist has come to rely on its availability or feels that, for him, it is an absolute necessity, he should continue to use it. I feel that the fluoroscope during colonoscopy, like the original string used for passage of the early instruments, is no longer necessary for successful colonoscopy. But if stiffener devices are used during colonoscopy, then fluoroscopy must be used.

Colonoscopic Landmarks

The following landmarks may be used to identify the location of various segments of bowel. The rectum is laced with multiple branching and interlacing thick, reddish blood vessels. The lumen is quite capacious and several large thickened semicircular folds are present. In the sigmoid colon these blood vessels become much finer and more diffuse. As the tip of the instrument enters the distal descending colon, a long tubular view of the colon is seen. Whenever a tubular view of the colon is observed with few interhaustral septae, this is descending colon (40). The transverse colon may be entered by directing the tip of the instrument in an abrupt left turn at the splenic flexure area. Frequently, a wide-open lumen into the transverse colon is not visible, and the location of the tip of the instrument can be ascertained either by observing the transillumination through the abdominal wall in the left upper quadrant, or rolling the patient onto the back and seeking the transillumination underneath the left lower rib cage. Endoscopically, the dome of the splenic flexure may appear as a blind pouch when the instrument is advanced directly up the descending colon. Once this blind pouch is entered, withdrawal of the instrument usually permits one to observe a thickened fold extending down from the superior margin of the cul-de-sac. This fold is a raphe with the dome of the splenic flexure present to its right and the superior margin of the distal transverse colon to its left. Because the junction of the transverse colon and descending colon frequently presents an acute angle pointed up toward the diaphragm one rarely can see down into the transverse colon at this point.

Controls should be rotated so that the tip is directed towards the transverse colon (to the left) and the instrument gently withdrawn in a jiggling maneuver. This not only straightens any sigmoid curves, but withdraws the bent tip from the dome of the splenic flexure and allows it to hook onto the lower lip of the acute angle into transverse colon and pull it inferiorly to permit a view into transverse colon. Once a segment of several centimeters of the transverse colon is visualized, the instrument can then be advanced into it. The lumen of the transverse colon is typically triangular in configuration since it is free in the transverse mesocolon and is surrounded by three teniae coli (*Fig. 11*). As the transverse colon is distended with air, the teniae coli act as limiting bands causing the triangular appearance. As the haustrae balloon out with air, their distension is limited by each interhaustral septum. The triangular configuration with the repetitive arched haustral pattern present a "gothic-arch" appearance to the transverse colon. The interhaustral septae become narrower at the angles of the triangles, and each succeeding triangular fold appears to be joined at its apex to the proximal and distal fold by a longitudinal thickening, representing the intramucosal configuration of the externally located teniae coli. The glow of the transilluminated light through the abdominal wall is frequently seen during passage through the transverse colon, thereby accurately locating the tip of the instrument. Another means of locating the tip of the instrument is by positioning the instrument so that the entire lumen is well visualized. The tip of the index finger of the right hand is then "poked" into the abdomen at several points. As the exploring finger presses on the bowel wall within view of the instrument, one can actually see an indentation of the colonic wall due to the finger. This can be seen even in obese patients, and exact location of the tip of the instrument can be ascertained. Intraluminally, as the instrument advances toward the hepatic flexure a dark bluish discoloration can be seen on the superior and left portion of the wall. This represents the liver, and the bluish color is due to its rich blood supply. To gain entry into the ascending colon, the instrument must be flexed again to the left and usually in a downward direction. Withdrawal of the instrument and clockwise rotation of the shaft permits entry into ascending colon. There is usually stool present in the ascending colon even if the patient has been adequately cleaned as far as this location. The type of stool is characteristic of ascending colon effluent, and has the consistency of gravy; no solid stool is present. The interhaustral septae in the ascending colon differ markedly from the transverse colon; they are not circumferential, are rounded and only encircle about 60 percent of the lumenal circumference. The ascending colon is much wider in caliber than the transverse colon. The ileocecal valve will be seen on the left and may appear as a small depression of the mucosa but is frequently hidden behind a thickened fold. Even in the obese patient, when the cecum is reached, the transilluminated light can be easily seen in the right lower quadrant (*Fig. 12*). Again, the pressure of an exploring finger may easily be seen to indent the colon, and pressure on the mid-abdomen may cause ileal effluent to empty into the colon, helping to identify the location of the ileocecal valve. The cecum itself may appear as a blind pouch or several large thickened folds may criss-cross the caput of the cecum.

Relationship of Colonoscopy to Barium Enema Radiographic Examination

The barium enema radiographic examination is the principal diagnostic test for examination of the colon. Radiographic examination is rapid, relatively comfortable for the patient, and can be used to screen a large group of patients. The ability of the colonoscope to visualize everything within the lumen of the bowel contours, as well as the capability to take biopsies and brush cytology of any lesion, renders it extremely valuable as an adjunct to the barium enema x-ray examination. If a suspicious area is seen on a barium enema x-ray, no longer is the patient required to be re-prepared and undergo either a second or third barium enema x-ray examination, but in those selected patients colonos-

FIG. 11. Typical triangular appearance of transverse colon.

FIG. 12. Transillumination of light through the abdominal wall with the tip in the mid-ascending colon.

FIG. 14. Nodular circumferential constricting carcinoma as seen in Figure 13. Notice reflection of light (highlights) from the nodules of the tumor edge.

FIG. 16. Smooth, yellowish appearance of the mucosa stretched over a lipoma seen in Figure 15.

FIG. 18. Smooth circumferential nodular indentations characteristic of colonic anastomosis. The color is the same as surrounding colonic mucosa.

FIG. 20. Adenomatous polyp with triangular configuration not seen on barium enema x-ray examination. Notice the hypertrophied interhaustral septae, tending to contract the lumen, characteristic of diverticulosis.

FIG. 23. Polyp found in patient whose x-ray is shown in Figure 22.

FIG. 27. Colonoscopy was performed on patient whose x-ray is shown in Figure 26. The large, yellowish nodule is a part of the carcinoma, as is the reddish nodule on the left. Biopsies revealed this to be adenocarcinoma of the colon.

FIG. 29. A small telangiectasia in the transverse colon.

FIG. 30. Multiple highlights reveal the irregularity of this mucosa revealing granularity. Notice the mild erythema. Biopsy forceps are present in the upper right-hand portion of the field.

FIG. 31. In ulcerative colitis ulcers are always discrete and occur in an area of inflamed mucosa.

FIG. 33. Multiple pseudopolyps caused the lumenal constriction demonstrated in Figure 32. No evidence of carcinoma was present. Pseudopolyps have a characteristic pathological picture and can be differentiated from carcinoma.

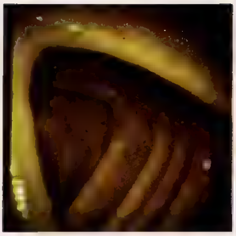
FIG. 34. Typical colonoscopic appearance of Crohn's disease with involvement of only one wall.

FIG. 35. Longitudinal serpiginous ulceration in Crohn's disease.

FIG. 38. Smooth rounded polyp with a broad base seen in the cecum. This was resected with the wire snare and cautery technique.

FIG. 40. Typical adenomatous polyp with reddish tip. The stalk fills the center of the field and is attached to the wall on the left.

FIG. 41. Typical appearance of polyp stalk following resection. Characteristically, no blood issues from the resected stalk following polypectomy and cautery.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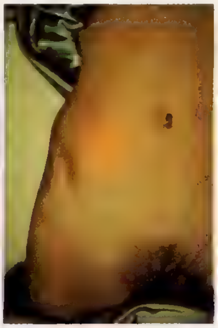
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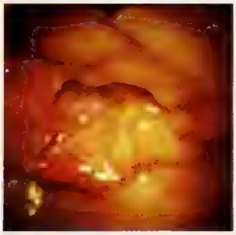
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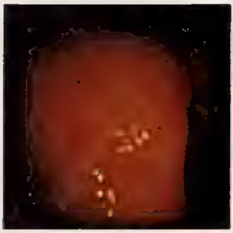
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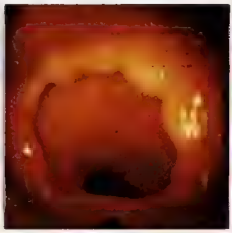
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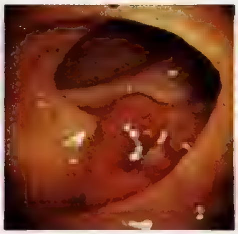
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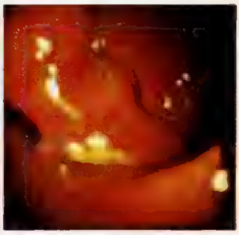
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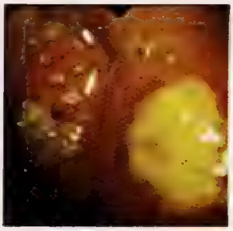
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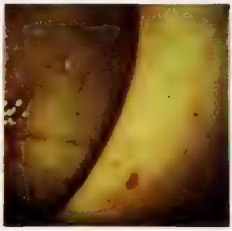
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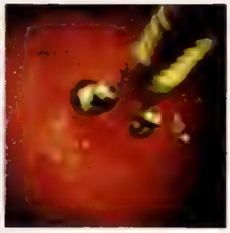
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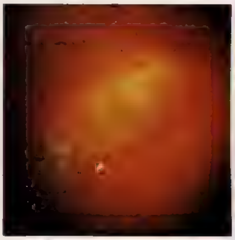
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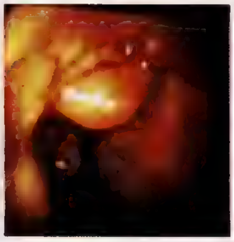
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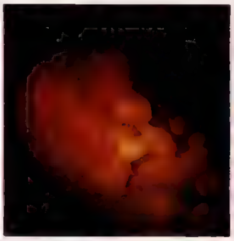
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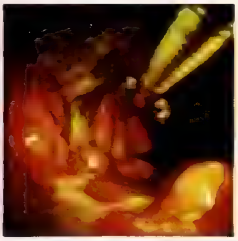
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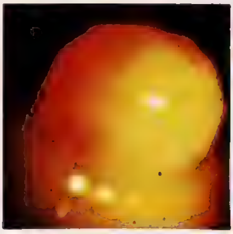
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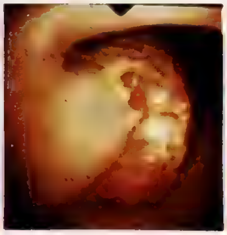
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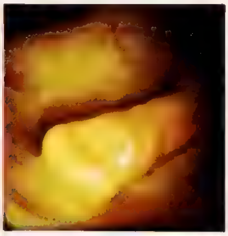
FIG. 41

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copy should be performed. If no lesion is found during colonoscopy the patient can be reassured. If a specific lesion is encountered it can be biopsied, brushed, or even removed through the instrument.

Not all colonoscopic examinations are performed with the intention of reaching the area of the cecum. The shorter instrument is easier to handle for the operator and is easier for the patient to tolerate. The medium instrument can be passed to the area of the mid-transverse colon in most instances. This is adequate for the greater majority of problems, since most of the colonic pathology exists in the left colon. If a specific lesion is seen in the right colon on barium enema x-ray examination, then the longer instrument should be used. In the event that the x-ray examination is negative and any problem such as persistent diarrhea or bleeding exists, colonoscopy should be performed with the long instrument, with the intention of reaching the cecum in search for a specific lesion such as a polyp, carcinoma, or colitis.

Depth of Insertion

The level of insertion of the colonoscope depends upon the type of pathology and the reason for the colonoscopy. If a specific lesion is sought and has been seen on the barium enema x-ray examination, the instrument appropriate to the level of the lesion should be used. The medium-length colonoscope can be inserted to the transverse colon, and the long instrument can be passed to the cecum. Most well-trained colonoscopists can reach the cecum with the long instrument in a high percentage of cases (12, 18, 44); however, a recent paper has described a success rate of only 26 percent if ancillary assistance such as internal or external stiffeners is not used (45). In my experience, in the last 200 colonoscopies performed attempting to reach the cecum without fluoroscopy or stiffeners, only two cases occurred in which the cecum could not be reached. Utilizing the techniques of jiggling and pleating the bowel upon the instrument, the cecum can be reached in approximately 15 to 30 minutes in over 90 percent of attempts, the remainder taking somewhat longer. The routine use of the long instrument is difficult because of its length, and the weight of the scope causes it to continually slip out of the rectum in a retrograde fashion.

The sigmoid colon can be passed in approximately 3 to 5 minutes in all cases which have not had previous pelvic surgery (which tends to fix the sigmoid loops and render passage more difficult), or in patients with diverticular disease where the bowel wall is markedly hypertrophied and fixed. The splenic flexure can be reached with the medium scope in approximately 90 percent of cases within 5 to 15 minutes.

Problems and Complications

Passage of the colonoscope through the sigmoid colon is extremely difficult in patients who have had previous pelvic surgery (18). Fixation of the bowel loops causes difficulty either in straightening the bowel or in making an alphaloop. In a nonoperated patient, the greatest difficulty encountered in passing the instrument is through an area of diverticulosis. In the presence of diverticular disease, the bowel wall is markedly hypertrophied, and relatively nondistensible. The interhaustral septae may tend to meet in the midline and the instrument may be directed into a large diverticulum which the examiner thinks is the lumen. Problems can be minimized if the examiner remembers to jiggle and pull back the tip of the instrument after each interhaustral fold has been passed. Diverticular orifices, even if large, can be recognized because they are perfectly round and have no folds leading into them. Thus, if a large round orifice is present in diverticulosis, and the scope cannot be passed into it easily, the tip must be withdrawn and the real lumen must be searched for. In the presence of diverticulosis, the usual landmarks for assistance at passage of the instrument are distorted and one cannot use "highlights" since highlights reflect from the openings of diverticular orifices as well as the bowel lumen. The thickening of interhaustral septae may give a triangular configuration to the sigmoid and descending colon, giving rise to a "pseudo-transverse colon" appearance. Negotiating sharp bends in the colon is not usually a problem in the unoperated patient, because they can be straightened out. If a cause for fixation is present, forceful pushing of the instrument may cause a perforation. Although perforations do occur during diagnostic colonoscopy, very few have been reported (14, 28, 46, 48). Perforations may occur in the hands of experienced operators as well as in the neophyte colonoscopist. Benign retroperitoneal emphysema has occurred following colonoscopy (49). This points out the need for the gentleness during the examination, and one must be aware that extreme care is necessary in the examination of patients with diverticular disease as well as inflammatory bowel disease.

Perforations performed with the tip of the instrument should be closed surgically because the perforation is at least 1 cm in diameter. If the perforation is small, it may be possible to handle it conservatively because of the precolonoscopic mechanical cleansing of the bowel with cathartics and enemas. I have perforated a colonic wall by extruding the biopsy forceps while the tip of the instrument was touching the colonic wall. I was not aware that the biopsy forceps had been extruded from the channel of the instrument, and only discovered the perforation when the entire forceps was passed through the colonic wall. A large amount of free air was present under the diaphragms on abdominal flat plate examination, but since the perforation hole was tiny (2–3 mm), the patient was managed conservatively with intravenous alimentation, antibiotics and a nasogastric tube. The patient did extremely well and did not develop any signs of infection or peritonitis. Perforation secondary to stiffeners has been mentioned before and has been reported recently. Thousands of colonic biopsies have been taken and I know of no cases of significant bleeding occurring in the normal patient. I had the experience of biopsying one patient with inflammatory bowel disease who bled slowly but persistently following multiple colonic biopsies and subsequent hematologic evaluation revealed the patient to have Von Willebrand's disease. I have had an interesting complication of colonoscopy when the endoscope was advanced inadvertently through an inguinal hernia into the scrotal sac and then, following the contour of the bowel, re-entered the abdominal cavity and up into the descending colon. Upon attempting to withdraw the instrument, the loop in the hernial sac became tightly coiled and could not be extricated. With gentle but forceful manipulation, the instrument became disimpacted from the hernia and was removed. Neither the patient nor the instrument suffered any harmful effects from the experience.

Therapeutic use of the endoscope has resulted in several complications. With the use of electrocoagulation current to remove polyps, a burn may be transmitted to the serosal surface (50) and cause a full-thickness slough of mucosa with perforation. Coagulation current can be transmitted to the tip of the polyp even though the snare is around the base. If the polyp tip is allowed to contact the opposite wall of the bowel, a spark-gap or burn may be transmitted to that wall with a resulting opposite-wall burn and perforation may occur at a site opposite the polypectomy. Bleeding has occurred following colonic polypectomy (8), even in the presence of apparently good burn of the pedicle. Such bleeding may be handled conservatively with bed rest and blood transfusions if necessary and may not require subsequent surgical intervention. An attempt should be made colonoscopically to re-snare the remaining pedicle of the polyp if bleeding is seen immediately following the polypectomy. Instillation of epinephrine (several cc's of 1/10,000 dilution) may assist in hemostasis, and ice-water enemas may be of some benefit.

It has been reported that air is delivered through the Olympus instrument with a higher pressure than through the ACMI instrument (47). This may theoretically lead to increased instances of perforation of a diverticulum should the scope be impacted into a diverticular orifice and distension attempted. I have not found this to be a problem.

Occasionally, a lesion may be visualized with the colonoscope, but the biopsy forceps cannot be extruded into the colonic lumen. This occurs when an acute angulation of the tip of the instrument is present. Usually this can be overcome if the instrument is withdrawn and the tip straightened; the biopsy forceps can then be passed. The forceps and biopsy channel may be lubricated with silicone prior to use. Occasionally, the biopsy forceps is extended, the lesion is in view but the jaws of the forceps may not open due to the convolutions of the small spring-wire that controls the forcep-opening mechanism. When this happens, a cytology brush can frequently be passed and cytologic specimens can be taken.

Cost of Colonoscopy

An individual colonoscope can be purchased for approximately $4,000.00 to $5,000.00. The longer colonoscopes cost about 10 percent more than the medium-sized instruments. The light sources which provide illumination can be purchased for approximately $700.00 for a small model, or a large console with a high intensity Xenon lamp may cost $5000.00. The side arm attachment which permits an observer/assistant to simultaneously view the lumen costs approximately one-third as much as the initial price of the instrument. Biopsy forceps which frequently become bent and unusable cost approximately $75.00. The snare wire for removal of colonic polyps may range in price from $3.00 (for the homemade snare) to $150.00 for a ready-made plastic-handled device. Electrocoagulation machines for operative use may be purchased from $500.00 to $1000.00. The instruments are fragile and may be easily rendered inoperable by even minor problems such as rupture of a plastic tube in the head of the instrument which is responsible for the air or suction facility. Fiber bundles may be broken by excessive bending or kinking of the instrument, and cables which run the length of the instrument to deflect the tip may be pulled off and require removal of the entire outer sheath of the instrument for their repair. Even relatively minor repairs may cost $200.00 to $300.00 and replacement of fiberoptic bundles may cost in the vicinity of $1000.00. It has been stated that each time the fiberoptic instrument is used between $10.00 and $25.00 (51, 52) should be set aside for repair, since that is the approximate order of magnitude of mechanical breakdown. One must be prepared to spend $1000.00 in repairs every 8 to 12 months.

It has been estimated that the length of hospitalization necessary for the removal of colonic polyps via the colonoscope was reduced by 66 percent over removal by laparotomy, and that neither an anesthesiologist nor recovery room care was needed for the procedure (8, 53). The total cost of a colonoscopic polypectomy is less than one-third of that required for removal of the same lesion by a transabdominal approach. The cost of the colonoscopic examination is further decreased by the performance of the examination in a setting outside the hospital, in a private office without fluoroscopy and without anesthesia.

Television monitors can be attached to the teaching side-arm, and project the intralumenal image to a remote television screen so that several observers can view the endoscopic aspect of the colon in the comfort of a classroom situation. The cost for the television apparatus is approximately $4000.00 and a video-tape machine for storage of information and replay facilities can be purchased for approximately $2000.00. A variety of cameras can be used to provide still or motion pictures, with expenses commensurate with the current price of 35 mm still cameras or 8–16 mm movie cameras.

Training in colonoscopy has largely been a self-taught process. Now, there are a number of individuals who perform the technique well and are willing to teach others. Few formal training programs exist, but each year dozens of physicians come to The Mount Sinai Hospital, as well as other centers (8, 54), to learn the fundamentals of the technique and return to their hospitals/clinics/offices to perfect their skills. A monograph and set of slides on colonoscopy is available (55) but nothing replaces a one-to-one preceptorship for mastering colonoscopy.

Diagnostic Colonoscopy

Investigation of abnormality seen on barium enema. Any lesion seen on the barium enema radiographic examination is amenable to direct visual inspection with the colonoscope. Not only can the lesion be observed, but biopsies may be taken from the surface of the lesion and brush cytology can be easily obtained.

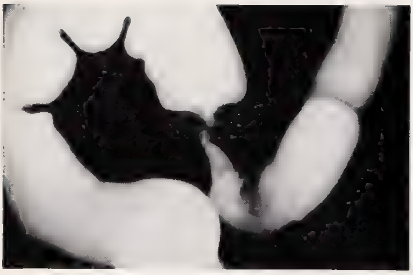

Fig. 13.

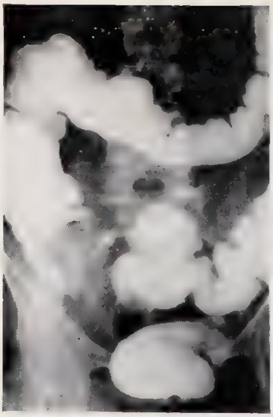

Fig. 15.

Fig. 13. Typical appearance of carcinoma of the sigmoid colon.
Fig. 15. Smooth indentation of the cecum.

The endoscopist can readily differentiate a polypoid lesion from retained stool on the surface, and evaluate strictures or narrowed segments anywhere throughout the length of the large bowel. Obvious lesions such as carcinoma (Figs. 13 & *14*) seen on x-ray need not be colonoscoped and biopsied, but other undetected pathology may be seen through the endoscope (8). Polyps may be seen in association with cancer (56–59) and be difficult to locate during laparotomy. Unusual conditions such as pneumatosis coli (60), ischemic colitis (61), and the "colitis of Behcet's disease" (62) may be seen and confirmed by colonoscopy. The long colonoscope is especially useful for inspecting the area of the cecum or ileocecal valve (17), a frequent site of lipomatous tumors. If the barium enema is suspicious for the presence of a lesion, colonoscopy can confirm or negate that suspicion.

The patient whose barium enema is shown in Figure 15 had recurrent abdominal cramps. The x-ray demonstrated an intussuscepting cecal lesion which was found on colonoscopy (*Fig. 16*) to be a lipoma of the cecum. Occasionally, especially in the postoperative patient, abnormalities may be seen which may represent surgical distortion without real pathology. In these instances, colonoscopy may help to solve the problem.

Case 1. The barium enema (Fig. 17) revealed a persistent filling defect in the area of the lower descending colon. The patient had a previous colonic resection for sigmoid carcinoma, and this examination was performed one year postoperatively because the patient complained of diarrhea. Colonoscopy revealed a normal anastomosis, with no evidence of recurrent tumor. A scar was seen in the area of the anastomosis. An intracolonic anastomosis usually has the appearance (*Fig. 18*) of smooth indentations along a ridge at the anastomotic line.

Case 2. A 62-year-old woman had recurrent bleeding per rectum, and barium enema (Fig. 19) demonstrated an anastomosis in the descending colon which had been performed 30 years ago for "colonic obstruction." Colonoscopy revealed carcinoma in the anastomotic site.

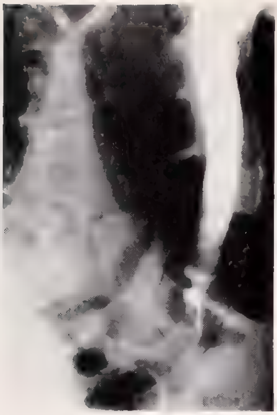

Fig. 17.

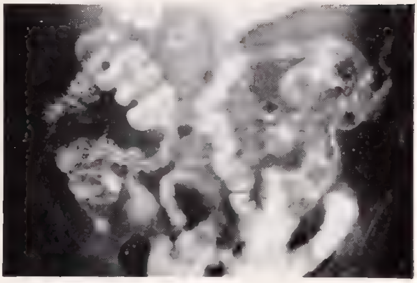

Fig. 19.

Fig. 17. Irregularity at the area of anastomosis one year following colonic resection for carcinoma.

Fig. 19. End-to-end anastomosis in the descending colon for "obstruction" 23 years previously. Colonoscopy revealed a carcinoma in the blind pouch with pseudodiverticulae.

Diverticulosis obscures many underlying lesions on the barium enema x-ray, and any patient who presents with rectal bleeding and has diverticulosis on x-ray should be endoscoped. *Figure 20* shows a small polyp which caused bleeding and was not evident on x-ray examination. Note the thickened interhaustral septae so characteristic of diverticular disease.

Case 3. A 67-year-old woman was admitted for bright red rectal bleeding. Two previous barium enemas revealed only the presence of diverticulosis. Colonoscopy was performed to determine the level at which diverticular bleeding had occurred, but a large (2.5 cm), flat adenocarcinoma was seen in the sigmoid colon. This x-ray (Fig. 21) represents the area in which the carcinoma was located. Even in retrospect it is not possible to make the diagnosis of a mass lesion because of the masking effect of the diverticular disease.

Case 4. A 50-year-old man was colonoscoped because of bright red rectal bleeding. Barium enema x-rays in the past had always been recorded as diverticulosis (Fig. 22).

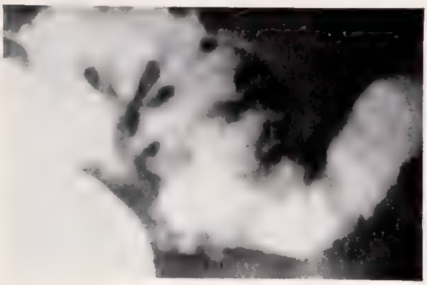

Fig. 21.

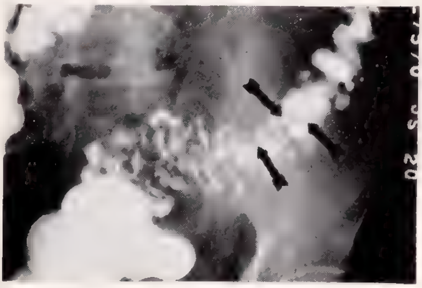

Fig. 22.

Fig. 21. Sigmoid colon with diverticulosis in a patient who presented with bright red blood per rectum. Colonoscopy revealed a carcinoma in this segment.

Fig. 22. Arrows outline a polyp found during colonoscopy in a patient with diverticulosis and bright red blood per rectum. Diverticulosis tends to mask intralumenal pathology.

Colonoscopy revealed a 1.0 × 2.0 cm polyp in the descending colon (*Fig. 23*) which was recognized on the x-ray only in retrospect following the discovery of the polyp. The polyp was resected colonoscopically and the patient has not had any further bleeding episodes.

When diverticulosis and carcinoma coexist, the differential diagnosis may be difficult radiographically, but can be made with assurance colonoscopically.

Case 5. A 62-year-old man had the acute onset of fever to 103 degrees with tenderness in the left lower quadrant. A mass was palpable and the barium enema revealed (Fig. 24) diverticuli and narrowing in the sigmoid colon. The diagnosis was acute diverticulitis, and a colonoscopic examination was performed which revealed a large, bulky, friable nodular tumor mass evident within the lumen, causing intralumenal narrowing.

The radiographic finding of complete obstruction to the retrograde flow of barium frequently poses a difficult differential diagnostic problem for the radiologist. The radiologist cannot be sure whether the tapered end of the segment is secondary to an inflammatory lesion such as diverticulitis or to a carcinoma. The use of colonoscopy has permitted us to be accurate in every case that we have been called upon to endoscope. Figure 25 reveals narrowing of the lumen secondary to diverticulitis. Endoscopically, the bowel tapered down to a smooth narrow opening, and pus was seen in the lumen. The instrument could not be passed into the narrowed segment. Figure 26 also represents a case of complete retrograde obstruction to the flow of barium and here, colonoscopy revealed a bulky, nodular carcinoma (*Fig. 27*) and biopsy showed adenocarcinoma.

Symptomatology with a "normal" barium enema. When pain is the major indication for a colonoscopic examination with a negative barium enema x-ray, a specific lesion is rarely found. In the patient with "spastic colon" in whom the barium enema shows some edema and "picket-fence" appearance of the sigmoid colon, the colonoscopist may see hypertrophy of the interhaustral septae, but no lesions are usually evident. Colonoscopy in the presence of massive colonic bleeding is usually not indicated, because the bowel is unprepared. The presence

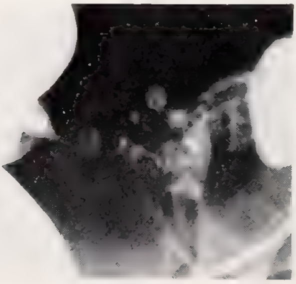

FIG. 24.

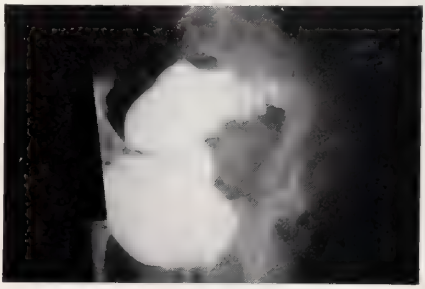

FIG. 25.

FIG. 24. Narrowing of the sigmoid colon with diverticuli present. The diagnosis of carcinoma was made during colonoscopy when a friable, bulky, nodular tumor was seen and biopsied in this area.

FIG. 25. Smooth tapering of the sigmoid in a patient with complete retrograde obstruction to the flow of barium. Endoscopy revealed a smooth tapering with no intralumenal tumor.

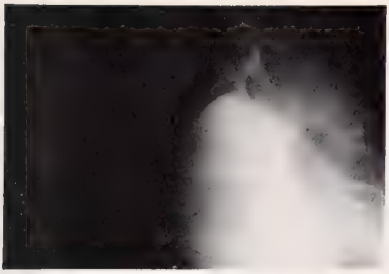

FIG. 26.

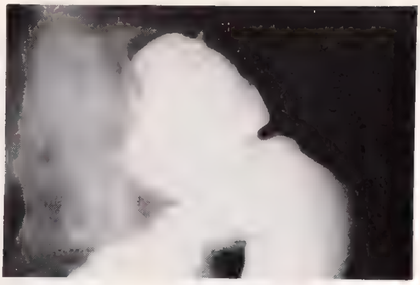

FIG. 28.

FIG. 26. Complete retrograde obstruction to the flow of barium in the sigmoid colon. See Figure 27.

FIG. 28. The splenic flexure in a man with rectal bleeding for one year. The extreme tortuosity of the splenic flexure rendered x-ray visualization difficult. Colonoscopy revealed a flat saucer-shaped carcinoma as the etiology of rectal bleeding.

of stool or large clots of blood may render colonoscopy ineffective. Whenever bright red blood is passed per rectum, a sigmoidoscopy and barium enema should be performed, but that may not resolve the problem of etiology. I have colonoscoped several patients who were thought to have bleeding "above the reach of the sigmoidoscope" who were actually bleeding from hemorrhoids. The actual diagnosis was only revealed when examination of the colon revealed no proximal bleeding, and blood was seen in increasing quantity as the instrument was withdrawn into the rectum. In unusual circumstances, colonoscopy can be of benefit during massive bleeding.

Case 6. A 32-year-old woman was seen for recurrent episodes of bright red rectal bleeding over the past 5 years. She had four episodes of bright red rectal bleeding and two colonoscopic examinations performed after the bleeding had subsided failed to reveal any site of blood loss. Multiple upper and lower GI x-rays were normal. She was admitted to the hospital at this time because of massive bright red rectal bleeding one year following her last episode. After the bleeding had subsided, she was being prepared for an interval colonoscopy when massive bleeding recurred in the hospital. Because the bowel was clean, the long colonoscope was passed (with some difficulty) to the area of the cecum. It was noted that blood was issuing through the ileocecal valve and an immediate exploratory laparotomy was performed since the colon was then excluded as the bleeding site. At operation, a short segment of regional enteritis was found, resected and and was responsible for the bleeding. The patient had no symptoms referable to this diseased segment other than bleeding.

When recurrent rectal bleeding is the indication for colonoscopy in the absence of a specific lesion on the barium enema, pathologic conditions have been reported (63) in 26 percent of cases (14); but I have found a greater yield, approximately 50 percent of cases. It must be mentioned that this is a selected series and I do not see all patients with bright red rectal bleeding. It is possible that I am requested to colonoscope those patients in whom a high "index of suspicion" exists for the presence of a specific lesion.

Case 7. A 62-year-old man had three barium enemas during the past year for rectal bleeding. No abnormalities were seen on any of the barium enema examinations (Fig.

28). Colonoscopy was performed and a small flat, saucer-shaped carcinoma was found in the splenic flexure area of the colon. Biopsy revealed this to be an infiltrating adenocarcinoma, and at surgery, the carcinoma was transmural and involved the serosal surface of the bowel.

Case 8. A 34-year-old woman was seen with chronic anemia and intermittent red blood mixed with the stool. All routine diagnostic modalities were unrevealing and colonoscopy demonstrated several discrete telangiectases (*Fig. 29*). These small, round angiomas present a characteristic endoscopic appearance.

Case 9. A 65-year-old woman underwent an ileotransverse colostomy for carcinoma of the hepatic flexure area of the colon, 2 years previously. She presented with bright red rectal bleeding, and 2 barium enema x-ray examinations were unrevealing. The surgeon was convinced that the patient had carcinoma at the site of the previous resection, and requested colonoscopy prior to exploratory laparotomy. Upon insertion of the scope into the junction of the sigmoid and descending colon, a small bleeding tumor was found. Biopsy proved the diagnosis to be carcinoma, and the patient had a subsequent sigmoid resection without the presence of local nodal metastases.

Inflammatory bowel disease. In the differential diagnosis of inflammatory bowel disease, histopathologic examination of the mucosal biopsy specimens is of little benefit unless granulomata are seen (8, 64). Radiographic examination and the clinical course of the patient have been the major differential points in deciding whether the patient has granulomatous or ulcerative colitis. Colonoscopy is a new diagnostic modality, and appears to be as accurate as radiography in establishing the differential diagnosis between the two forms of colitis. The addition of direct inspection of the mucosa and the capability of taking biopsies may render endoscopy more useful in making that differentiation.

The earliest endoscopic pathology in ulcerative colitis is a loss of the normal mucosal vascular pattern (*Fig. 30*) (65). Erythema and granularity are frequent. A hallmark of ulcerative colitis is that ulcers tend to be discrete and always occur in a bed of abnormal inflamed mucosa (*Fig. 31*). Pseudopolyps may reach large dimensions, and cause narrowing of the lumen (Figs. 32 and *33*).

In granulomatous colitis, the disease process is not continuous as it is in ulcerative colitis, and one may see a segment of normal bowel interspersed between abnormal areas, or involvement of one wall of the colon with no abnormality of the adjacent wall (*Fig. 34*). Ulcerations may occur in a longitudinal serpigenous fashion, and may be seen in areas of apparently normal mucosa (*Fig. 35*). Both ulcerative and granulomatous colitis may develop pseudopolyps, but "cobblestoning" is only seen in Crohn's disease. With cobblestoning, the base of the mucosal elevation is wider than it is tall, where in pseudopolyps, the opposite is true. In both diseases, the interhaustral septae are thickened and blunted, and both may have strictures (Fig. 36) and lumenal narrowing. The extent of the disease may be greater than is evident radiographically (14, 66, 67), and frequently, in granulomatous colitis, one may see ulcerations and mucosal edema in the sigmoid where x-ray may only show involvement of the transverse colon or splenic flexure area. Precise definition of colonic involvement is quite necessary when surgery is contemplated. A recent

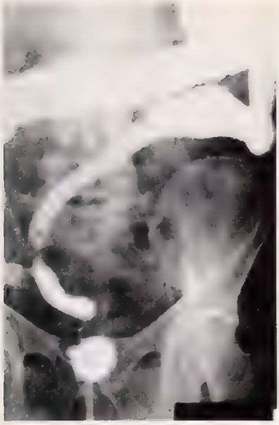

FIG. 32.

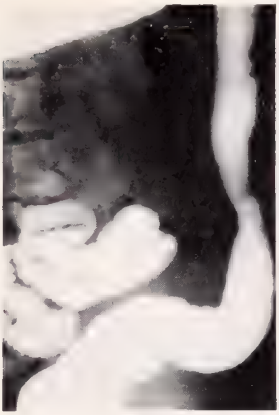

FIG. 36.

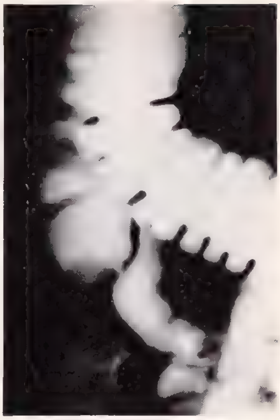

FIG. 37.

FIG. 32. Narrowing in the area of the sigmoid colon in a man with long standing ulcerative colitis. The differential diagnosis included carcinoma.

FIG. 36. Stricture in the descending colon in a patient with granulomatous colitis. Colonoscopy revealed the stricture to be caused by a large ulceration. No evidence of carcinoma was present.

FIG. 37. Filling defect in the cecum found on a barium enema performed for diarrhea. The endoscopic field is seen in *Figure 38*.

report demonstrated that 50 percent of patients with "ulcerative proctitis" who were colonoscoped had microscopic evidence (on biopsy) of colonic inflammation extending up to the splenic flexure area of the colon (68).

Three patients with Crohn's disease of the colon revealed previously undiagnosed amyloidosis (69) during review of our colonoscopic biopsy material.

Therapeutic Colonoscopy

Removal of polyps colonoscopically at The Mount Sinai Hospital have been established as a team effort. A nurse/assistant is present, a surgeon (Dr. Albert Frankel) and myself have been involved in the removal of colonic polyps over the past two and a half years (70). We have removed over 500 polyps from the colon, and only one patient required exploratory laparotomy because of peritoneal signs that developed following the polypectomy. This patient had a large polyp and several burns were made to remove this polyp. Because of the presence of peritoneal findings, 6 hours postpolypectomy, the patient had exploratory laparotomy and a whitish burn on the serosal surface of the bowel was seen at the site of the polypectomy. The area was plicated without bowel resection and the patient made an uneventful recovery. Bleeding has been encountered in 5 of the patients, but usually of slight degree. One patient required 2 units of blood and one patient required 4 units. The patient who required 4 units of blood was on anticoagulants at the time to prevent thrombosis of an aortic valvular prosthesis. His level of anticoagulation was rapidly corrected, and attempts were made to re-coagulate the bleeding vessel at the time of colonoscopy. Bleeding subsided within a few hours of the colonoscopy, follow-

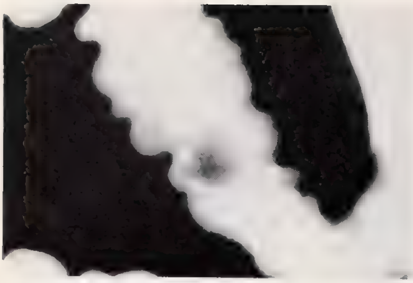

FIG. 39. Polyp on a pedicle in the sigmoid colon. The endoscopic view is seen in Figure 40.

ing the use of ice-water enema lavages. Sessile polyps as well as pedunculated lesions can be successfully removed colonoscopically (39, 71–77) (Figs. 37 & 38). We have successfully resected polyps of the colon as large as 6 cm in diameter. A wire snare is manipulated around the head of the polyp and tightened upon the stalk of the polyp. Electrocautery current coagulates the blood vessel in the stalk of the polyp and severs the polyp from its attachment to the wall (Figs. 39, *40*, *41*). CO_2 is insufflated for polypectomy by several physicians (18, 78), but we do not use CO_2 and know of no explosions during fiberoptic colonoscopic polypectomies. This reflects the experience of others (8, 79), and experimental studies on measurements of colonic gas show that with adequate preparation and a clean bowel, critical explosive levels are never reached (80, 81). Ninety-seven percent of all polyps resected have been recovered. A wire basket device has been introduced to grasp the polyps for removal, but I find it cumbersome to use. The technique most commonly used is to place the tip of the instrument on the severed polyp and, applying suction, to withdraw the scope and the polyp together. Vision is occluded by the polyp, and the instrument is re-inserted for inspection of the remainder of the colon or removal of further polyps. Approximately 10 percent of the removed polyps over 1 cm in diameter have some evidence of cellular atypia, in situ carcinoma or invasive carcinoma (82). Eight patients have had formal exploratory laparotomy following the removal of a radiographically benign-appearing polyp which was reported as revealing "deeply infiltrating adenocarcinoma" on pathologic examination. In none of the patients has there been any evidence of residual carcinoma nor have any patients had any nodal involvement with the carcinoma. The removal of colonic polyps by this procedure is a feasible, safe procedure with low morbidity. The necessity for formal laparotomy and surgical removal of polyps is becoming rare since lesions can now be removed at any point from the anus to the ileocecal valve.

Among other therapeutic uses of the colonoscope is reduction of volvulus occurring in the colon. An Ewald tube can be taped to the colonoscope and maneuvered to the area of the volvulus under direct vision. As the tip of the instrument traverses the twisted segment, immediate evacuation of copious quantities of air and liquid fecal material occurs with complete reduction of the volvulus. This procedure is not difficult, and could be a useful adjunct to the therapy of such conditions.

Summary

The entire colon can now be completely visualized from the rectum to the cecum. Instrumentation and techniques are continually improving and most physicians can learn to intubate the colon successfully. The results are rewarding in terms of diagnostic ability and in terms of therapeutic potential for the patient. Thousands of polyps have been successfully removed without exploratory laparotomy and its attendant morbidity and hospitalization costs. Diseases can be studied, the effect of drugs can be assessed, and the era of therapeutic endoscopy is in its infancy.

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Endoscopic Visualization of the Pancreatic and Biliary Ducts

JEROME D. WAYE, M.D.

Radiologic visualization of the biliary duct system by the intravenous cholangiogram is a well-established technique. The major portion of the common bile duct can usually be visualized in the nonjaundiced patient following an intravenous injection of a suitable contrast material. The intrahepatic branches of the biliary tree cannot be seen even if tomography is used. Radiographic visualization of the pancreatic ductal system with a fluoroscopically guided cannula has been attempted (1) but has not met with consistent success. There is no contrast material which concentrates within the ductal system of the pancreas. A technique is now available which, with a high degree of success, permits excellent visualization of the extrahepatic as well as intrahepatic biliary tracts in the intact patient, whatever the level of serum bilirubin. The procedure can also afford opacification of the entire pancreatic duct and its major branches as well as the accessory duct of Santorini. This approach is essentially an endoscopic procedure during which contrast material is injected into the papilla of Vater under direct vision. Terminology has been confusing but herein it shall be referred to as "endoscopic retrograde cholangiopancreatography" (ERCP).

This review is intended to acquaint the physician with one of the newest advances in gastrointestinal endoscopy, and evaluate ERCP in view of the current literature, with observations based on personal experience. In November of 1972, I journeyed to Japan where much of the pioneer work has been performed concerning ERCP. Upon my return, Dr. Jack Vennes demonstrated further aspects of the procedure to me, and I have since completed over two hundred ERCP's.

Instrumentation

Two instruments are currently capable of providing the operator with the ability to cannulate the ampulla of Vater. One is manufactured by the Machida Endoscope Company, Ltd., but is not currently available in the United States. The instrument routinely used in this country is the Olympus JF-B endoscope, available through the Olympus Corporation of America (Fig. 1). The instrument is 10 mm in diameter and quite flexible. The distal 4.5 cm portion of the instrument can be rotated through a full circle of 360 degrees by controls on the proximal end. The working length of the instrument is 137.0 cm; the viewing port is at right angles to its length and the angle of view is 65 degrees. The right angle vision is important to enable the apex of the papilla of Vater to be seen directly as it protrudes into the duodenal lumen. A forward viewing instrument provides only a tangential view of the mound of the ampulla of Vater, and the

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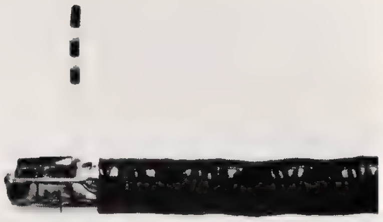

FIG. 1. Lateral JFB2 Olympus gastroduodenoscope. The cannula is deflected at 90° to the long axis of the instrument to permit insertion into the papilla of Vater.

small orifice at its apex can neither be seen nor cannulated. A Teflon® catheter (1.5 or 1.7 mm in diameter) can be inserted through the entire length of the instrument and the angle at which it protrudes from the distal tip is controlled by a lever mechanism on the proximal instrument head. If the catheter is removed, a cytology brush or biopsy forceps can be passed if desired. The cannula has a tapered tip but may be specially ordered with a tiny metal tip which some endoscopists (2, 3) feel is useful in negotiating the papillary orifice. All cannulae are being manufactured with millimeter markers on the distal 6 mm so that one can know the exact distance the cannula has been inserted into the papilla.

The Olympus JF-B was originally developed as a gastroduodenoscope and can provide excellent views of the stomach. The esophagus is difficult to examine adequately because the angle of vision is not parallel to the long axis of the esophagus, but is at right angles to it. Because of the small size of the biopsy/cannula channel, biopsy specimens are tiny but diagnostic.

Light is provided by various sources external to the endoscope and transmitted to the lumen by incoherent, nonoriented fiber bundles. Water can be sprayed over the distal lens for cleansing during endoscopy, and control buttons are provided for air insufflation and suction.

A teaching attachment can be affixed to the eyepiece which permits intralumenal visualization for an observer. Still and movie film can be taken through the instrument for permanent documentation and teaching purposes.

Indications

The differential diagnosis of jaundice has long been a perplexing problem, the solution of which can be provided by ERCP. The presence of jaundice usually precludes routine dye studies of the biliary tract. Transhepatic cholangiography with danger of hemorrhage or bile leak through the punctured liver capsule has been the only nonsurgical means of ascertaining the existence of an actual obstruction to the flow of bile when blood chemistries are indicative of obstruction. Exploratory laparotomy is to be avoided under these circumstances because several medications are known to cause the clinical picture of intrahepatic cholestasis with blood chemistries paralleling those in extrahepatic obstruction. A liver biopsy may be hazardous in the differential diagnosis of these two conditions, but retrograde injection of dye into the biliary tree frequently solves the problem directly.

Patients allergic to contrast material who have pain in the right upper quadrant suggestive of biliary tract disease may tolerate the intraductal injection of dye into the biliary tree without allergic responses. In the allergic patient caution should always be advised, but I have performed ERCP in three such patients without untoward responses. There is no mention in the literature of any similar experience with allergy to contrast media.

Patients with chronic pancreatitis or those with documented recurrent pancreatitis in whom surgery is contemplated may benefit from demonstration of the anatomy of the pancreas prior to pancreatic surgery. Strictures or pseudocysts within the pancreas can be documented with pancreatography. Demonstration of a normal biliary tree effectively rules out pathology of that system, but demonstration of a normal pancreatic duct does not imply that the pancreas is normal. An abnormal pancreatogram may substantiate a suspected pancreatic abnormality, but since only the duct is visualized, pancreatic acinar function may be compromised in the presence of a normal-appearing duct. Radiographic abnormalities of the pancreas obtained by ERCP correlate poorly with functional testing (2).

Preendoscopic Medication

A wide variety of medication has been used to ensure that the duodenum is in a completely atonic state when the papilla of Vater is located. Any peristaltic or contractile motions of the duodenum will result in cannulation failure since a 1-mm error in catheter adjustment will prevent entry into the ampulla. Cholinergic blockade both of long and short reflex arcs can be readily accomplished without significant side effects. The technique that I use is as follows: the patient receives no medication prior to entering the fluoroscopic unit. While lying on the x-ray table, atropine, 0.6 mg and propantheline bromide, 15 mg, are given intramuscularly. The two anticholinergic medications appear to have an additive effect and the atropine tends to reduce oral secretions. Excellent peristaltic cessation is obtained with a combination of the two drugs. A butterfly scalp-vein needle is inserted into the right forearm and 10–15 mg diazepam is injected intravenously followed by a saline flush. The syringe containing saline is taped to the forearm, permitting administration of other medication during the procedure if necessary. A small amount of 2% viscous xylocaine is placed in the posterior pharynx and the patient is requested to swallow it. The red color of this material does not alter the endoscopic findings in the stomach. The patient is then rolled over into a left anterior oblique position with the left arm stretched out alongside the body. The right arm is flexed at the elbow and serves to stabilize the patient's position. The instrument is then passed through the cricopharynx. Once the duodenum is entered, glucagon may be given intravenously in 0.5–1.0 mg increments to achieve duodenal atony, although with the combination of drugs previously mentioned I have not found glucagon necessary. No patient in this series has had any side effect to the anticholinergic medication.

Hyoscine n-butyl bromide (Buscopan®) given in 40–80 mg doses intramuscularly or intravenously is a widely used antimotility drug for ERCP (4, 5) but is not available in the United States. A similar agent, trihydroxy propiophenone (Cospanon®) (2) is said to produce relaxation of the musculature of the ampulla of Vater, but also is not available in this country. Dicyclomine HCl (Bentyl®) in doses of 60–80 mg intramuscularly has been successfully (6) used for relaxation of duodenal smooth muscular activity. Large doses of atropine, up to 4 mg intramuscularly, have been stated to produce the desired atony as well as to relax the ampullary muscle (7). Several investigators have used meperidine in small doses (35–50 mg) in the preparation of their patients. The use of general anesthesia (8, 9) has been reported in the early experience of ERCP, but is no longer necessary. Light sedation is sufficient for most cases, and the patient who is relaxed but awake can assist during the procedure by rolling onto the side or to the prone position.

Technique

The patient is prepared as for routine upper gastrointestinal endoscopy. The procedure should be explained to the patient, but often the reason for the examination is quite obvious to the patient since most ERCP's are performed for the presence of jaundice or abdominal pain. In some institutions (10, 11), ERCP is one of the first diagnostic tests applied to the patient with jaundice, but in most hospitals the ERCP is at the end of a long line of diagnostic procedures. Because of this, the patient is usually anxious to cooperate with the physician during the examination. After a 10–12 hour fast, dentures are removed and the patient is requested not to bite the instrument during its passage.

With the patient in the left anterior oblique position, after preendoscopic medication has been administered, a biteplate is placed between the teeth. The head of the instrument is held in the left hand, and the thumb is used to control the tip deflection and bend it along the posterior pharyngeal wall. The right hand grasps the shaft of the instrument and introduces it to the area of the cricopharynx. As the patient swallows, the smooth blunt endoscope is passed through the cricopharyngeal sphincter into the stomach with ease. The stomach is briefly inspected and the pyloric orifice identified. A thorough endoscopic examination is not indicated since cannulation is the major object of the procedure. If time permits, observation may be performed after the ERCP, but is usually more satisfactory if scheduled as a separate examination. As the pylorus is approached, the instrument must be manipulated so the pyloric orifice is viewed directly end-on, not tangentially. The tip is deflected downward and the smooth end of the instrument passes through the pylorus in blind fashion since the lateral view is occluded during that moment. Air is insufflated into the duodenal bulb and the shaft of the instrument is rotated in a clockwise direction 180 degrees (7). This brings the viewing port of the instrument around the first portion of the duodenum and allows visualization of the entire descending duodenum. Frequently, this maneuver places the instrument directly over the papilla of Vater. If the papilla is not immediately identified, the endoscope is passed down the descending duodenum; manipulation of controls allows movement of the tip in a circular fashion as the instrument is withdrawn up the duodenal sweep. The papilla will be located at approximately the 10 o'clock position and the shaft of the instrument must then be torqued (twisted) to allow direct en face visualization of the ampullary orifice. The technique of pancreatic cannulation was first reported by McCune (12) in 1969, but was developed into a feasible procedure by several Japanese groups (13–20). Japanese endoscopists seem to favor cannulation with the patient in the prone position, but some have performed cannulations in the supine or left lateral position. Rotation of the instrument within the duodenal sweep may be somewhat difficult and if the endoscope cannot be positioned so that the papilla lies in the same plane as is described by the arc of the cannula, successful entry cannot be accomplished. Because it is difficult to torque the endoscope shaft into a proper position with the tip of the instrument near the papilla, changing position (11) of the patient from right-lateral to prone or to supine may be helpful in achieving a better cannula-papilla position. With the left hand holding the head of the instrument, and the controls in a locked position, the cannula is pushed into the lumen with the right hand. The clean but nonsterile Teflon cannula is filled with contrast media before it is inserted into the instrument so that dye does not spill into the duodenum where it may stimulate peristalsis (2). A syringe with contrast remains attached to the cannula to exclude air from the system lest it be injected and appear on radiographs simulating a small stone. All cannulae are provided with a stiffener wire stylet of sufficient length that, when passed through the proximal portion of the cannula, prevents the cannula from kinking when force is used to extrude the cannula against the pressure exerted by the distal deflecting bridge. If the cannula enters the duct system with the stylus in place, its withdrawal leaves a column of air which is then injected into the system with the danger of artifact production. This can be circumvented by not using the stylet.

The thumb of the left hand manipulates a lever which changes the degrees of elevation of the catheter tip. Considerable endoscopic expertise is necessary to insert the cannula into the papillary orifice, as the technique of ERCP is the most difficult of all current endoscopic procedures. Once the cannula is inserted into the papilla, fluoroscopy is begun and a small amount of radiopaque contrast media is injected under continuous fluoroscopic control. A variety of contrast materials is available; a dense media is useful for the pancreas, but may obscure small stones in the common duct. 50–70% Renografin® or Urografin®, 50% Hypaque®, 50% Angiografin® or Conray 280® have all been used. There is no real difference in any of these agents used for ERCP, and saline may be injected into a partially filled, dilated common duct to further dilute the media used. Only 3–5 cc of contrast media are required to fill the entire pancreatic duct, and over-distension may cause dye to be extruded into the small acinar structures. The common bile duct may fill simultaneously with the pancreatic duct or the cannula may be repositioned into the common bile duct and contrast media injected under fluoroscopic guidance. Up to 40 cc of media may be used to fill the biliary tree if the gallbladder reservoir is present (3). Once the appropriate duct has been filled, x-ray films may be taken to verify the pathology seen. Since the normal pancreatic duct empties rapidly, films should be taken of the pancreatic duct while the instrument and cannula are in place. The biliary tree takes 15 to 30 minutes to empty, and the instrument may be withdrawn before x-rays are taken. X-rays should be taken prone, supine and in both obliques so that dye in the duodenum (which is frequently filled during the examination) will not obscure the pathology in the ductal systems. Patients may complain of mild abdominal pain while the pancreatic duct is being filled. Overfilling is avoided by continuous fluoroscopic monitoring, an extremely important part of the endoscopic retrograde cholangiopancreatogram. Fluoroscopy may cause damage to the fiberoptic bundles with yellowing, and most fiber bundles require replacement after approximately 100 retrograde studies. The time required for the ERCP varies from a few minutes to over 90 minutes. If the papilla is found easily and cannulated the examination can be successfully completed in a short time. In cases where difficulty is encountered in adjusting the position of the instrument, the cannula or the patient, even if the ampulla is visualized, or if one duct is filled but the desired duct cannot be filled, the examination may take over one and a half hours and still be unsuccessful.

Landmarks

Once the pylorus has been passed, the instrument enters the duodenal bulb, characterized by absence of mucosal folds. The typical circular fold pattern of the small bowel can be seen beginning at the apex of the duodenal bulb and the instrument must be passed beyond the superior knee of the duodenum to enter the descending portion. Following rotation of the instrument, a tubular view can be seen down the descending duodenum. With the patient in the left lateral position, the endoscope is rapidly passed down the descending duodenum and then slowly swept upward, using the right-left and up-down control mechanisms to scan the walls. The folds in the duodenum are arranged circularly, and tend to cross in an irregular fashion. The papilla will usually be seen at the 10 or 11 o'clock position as the endoscope is moved in a retrograde fashion up the descending duodenum. The ampullary mound is slightly posterior on the medial wall and is at the junction of the upper and middle third of the descending duodenum, about 6 cm distal to the bulb (6). Fluoroscopy will assist in locating the approximate position of the tip to the area of the papilla although the papilla cannot usually be identified with the simple air contrast study. I have found the papillary orifice as far distal as the inferior knee of the duodenum, and as proximal as the junction of the duodenal bulb and descending duodenum. When the ampullary orifice is located at the bend of the superior knee of the duodenum, positioning of the instrument and entry of the papilla is quite difficult since the distance from the lens to the orifice may be quite short, leaving little room for manipulations. Recognition of the papilla is simple when it is large and protrudes from the duodenal wall but a small (3 mm) button-like orifice may be hidden behind a fold and can be quite elusive. The location of the papilla may be heralded by a short (1–2 cm) longitudinal fold parallel to the long axis of the descending duodenum. Observation of this fold will usually demonstrate the papilla at its proximal end. The papilla may be buried under a transverse fold, which acts as a hood or cover over the papillary orifice. Muscular contraction within the ampullary sphincter will cause the shape of the papilla to change during the examination from hemispherical, to flat, to protuberant (21, 22). If a duodenal diverticulum is present, the papilla is frequently adjacent to it (23, 24), or even buried within the diverticulum. Once the mound of the ampulla has been located, the orifice has yet to be identified. Frequently, no orifice is visible as such and the examiner must push the catheter into several areas on the mound of the ampulla with frequent injections of contrast media under radiographic monitoring to ascertain if a ductal system has been entered. Usually a fine whitish circular reticular pattern is present on the papilla, with the orifice in the center. In 19 percent of patients (2) a rosette is seen with the ampullary orifice in its center. The finding of this anatomic configuration renders cannulation quite easy. When the orifice is located on the tip of a finger-like ampulla, it may be quite difficult to enter because pressure with the cannula may only cause the elongated papilla to flop away, rendering entry difficult. If the instrument has been withdrawn to the area of the duodenal bulb and the ampulla is not seen, one must assume that the papilla is flat, and the instrument must once again be inserted to the distal descending duodenum, and gradually withdrawn, looking behind the "hidden portion" of each of the valvulae conniventes. The orifice may rarely appear as a tiny slit or a small reddish dot on the duodenal wall. Failure to locate a ductal orifice is frequent in postoperative patients with Bilroth II anastomosis, and less common in patients with duodenal deformity or diverticulum. I have noted that duodenitis in Zollinger-Ellison syndrome distorts mucosal architecture and obscures the papilla. As experience increases, the incidence of failure to locate the papilla decreases, but in 3 to 8 percent of ERCP attempts, the ampullary mound cannot be visualized (25–27).

Usually, only one duct orifice is present on the papillary mound. Occasionally, one may see two separate orifices for the pancreatic and biliary ducts. A small proximal mound indicates the opening of the duct of Santorini which usually cannot be cannulated.

A dilated common duct presents a bulge into the duodenal lumen proximal to the papilla; a pancreatic carcinoma may appear as an indentation distal to it. Biopsies may be taken of any pathology seen in the duodenum.

Once ductal opacification is attained fluoroscopically the patient is rotated to the prone position for commencement of x-rays.

Results

Cannulation success rate. Visualization of the clinically relevant duct is the measure of a successful ERCP. Almost all investigators have reported a higher success rate with growing experience (6). The degree of success of various groups performing ERCP is listed in Table I.

A primary, but rare cause of failure is inability to locate the papilla of Vater. Failure also is inevitable when the papillary orifice cannot be approached en face, but instead the cannula can only be positioned obliquely to the orifice (28).

The cannula has a tendency to enter the pancreatic duct (PD) first, because its course is almost at right angles to the long axis of the descending duodenum in a direct line with the exploring catheter. If the PD fills first and only one papilla is seen, the cannula should be withdrawn while contrast is slowly injected under fluoroscopic guidance. In the presence of a common ampulla, the common bile duct (CBD) may be opacified, during continued injection, or the cannula may be withdrawn and repositioned. Since the course of the CBD is more posterior and cephalad to the PD, the cannula should be flexed to enter the papilla almost parallel to the duodenal wall, with a slight counterclockwise rotation of the instrument to point the catheter posteriorly.

Opacification of both ducts is seen in about 30 percent of ERCP (11), and in my experience filling of both ducts occurred in 42 percent of attempts. These figures are lower than one would expect from the 85 percent reported incidence

TABLE I

Rates for successful cannulation (opacification of ductal system) differ from the rate of visualization of the clinically relevant duct. Investigators with reports prior to 1974 have performed greater numbers of examinations than listed, with higher rates of success.

Investigator	Year	% Successful Cannulation	% Visualization of Desired Duct		Total No. Patients
			Pancreatic	Biliary	
Blumgart (67)	1974	80	—	—	146
Classen Demling (68) Frühmorgen	1974	92	84	75	1848
Cotton (2)	1972	83	78	73	132
Fujita (69)	1974	91			666
Hajiro (40)	1973	82	79	79	64
Kasugai (28)	1974	93	89	89	687
Katon (11)	1974	87	72	73	100
Liguory (70)	1974	93	82	81	986
Nebel (36)	1973	90	78	73	60
Ogoshi (35)	1973	90	93	86	252
Oi (25)	1972	81			310
Safrany (23)	1973	85		78	336
Vennes (31)	1974	92		83	108
Vennes (71)	1973		79		88
Waye	1974	88	83	85	121

of a common ampulla (29) for the PD and CBD, but may be explained by the tendency of physicians to discontinue further attempts at ductal visualization if the desired duct is filled first. Separate orifices for each duct are present in 4 percent to 23.5 percent (2) of cases, but I have not encountered this variant.

In my series, 107 patients had 108 attempts at ERCP. In The Mount Sinai Hospital with its heavy emphasis on pancreatic disease, most patients were studied to ascertain the status of the pancreatic duct. During the second year of cannulation experience, 88 percent of patients had ductal visualization, and 82 percent had adequate demonstration of the desired ductal system. Two patients were cannulation failures but diagnostic successes, since in one a pyloric channel ulcer was seen which accounted for persistent abdominal pains, and in the other, a duodenal carcinoma was seen and biopsied.

Endoscopic cholangiography The entire biliary tree is frequently outlined by contrast media and includes (Fig. 2) common bile duct, cystic duct, gallbladder, both hepatic ducts and many fine intrahepatic biliary secondary and tertiary radicles. The size of the ductal system can be measured using a correction based on the known 1.0 cm diameter of the endoscope which appears in many radiographs close to the ducts.

Cholangiograms in jaundiced patients enable a definitive diagnosis to be made. Stones obstructing the duct are easily visible, and the dilated ductal system is obvious. Stones frequently are dislodged from their ball-valve location at the distal end of the CBD, and float in the mid-portion of the dilated duct (Fig. 3). Stones impacted in the duct may permit dye to pass beyond, and the ductal system can be seen to be distended proximal to it (Fig. 4). If complete obstruction to the retrograde flow of contrast is encountered, the differential diagnosis between stone and carcinoma is made by the appearance of the site of

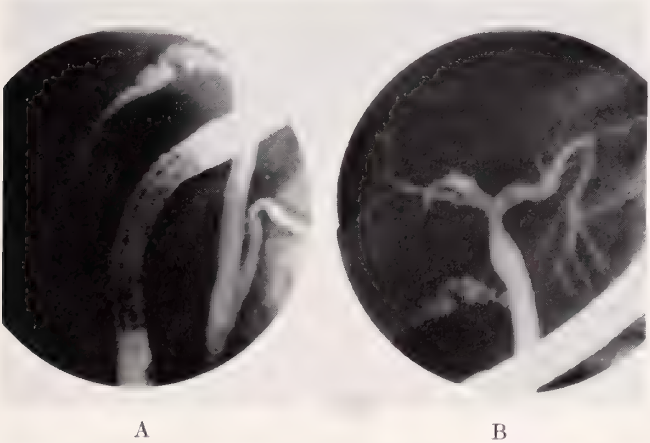

FIG. 2A. Lower portion of common bile duct, with pancreatic duct adjacent to it. The spiral valves of Heister can be seen at the upper portion of the field. The gallbladder is incompletely filled. The endoscope passes obliquely across the field.

FIG. 2B. Upper portion of common bile duct showing intrahepatic bifurcation and intrahepatic radicles.

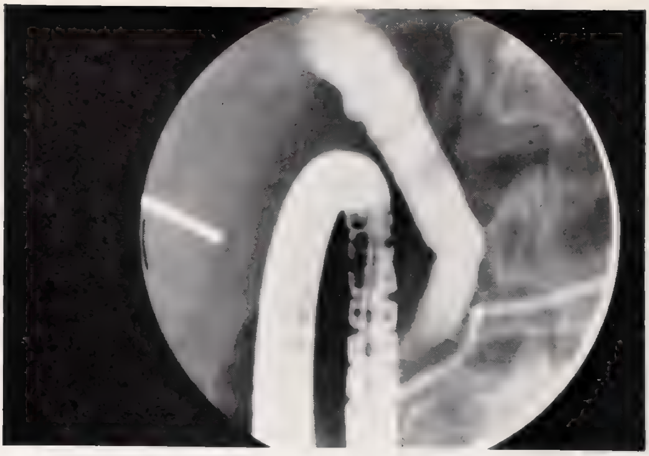

FIG. 3. Stone in common bile duct. Note position of stone in duct, dislodged by retrograde injection of contrast material. By comparison with the size of the endoscope (10 mm) accurate size of the common duct can be measured as 12 mm. Note pancreatic duct in the field.

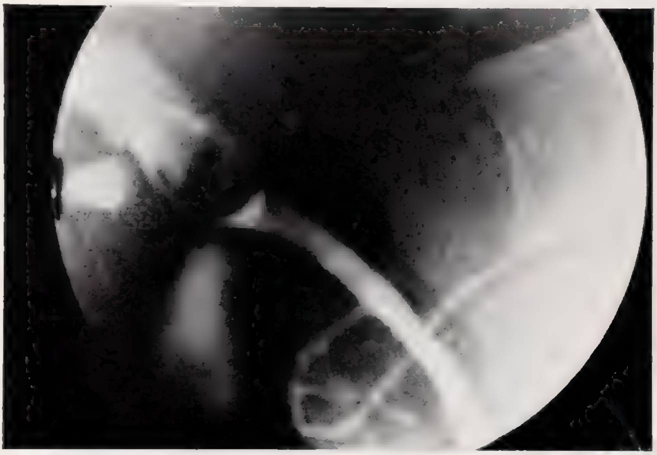

FIG. 4. Large stone impacted in common bile duct, which is dilated proximally. The gallbladder and pancreatic duct are filled.

obstruction; a meniscus will be present around a stone, but an irregular or rattail appearance is seen with carcinoma (Fig. 5). The length of an obstructing carcinoma can be determined by simultaneously filling the CBD from above via percutaneous transhepatic cholangiography (30).

A normal cholangiogram in a jaundiced patient indicates no major duct obstruction (31) and the diagnosis of liver disease can be made with confidence (Fig. 6), and a liver biopsy may safely be performed. In patients with primary biliary cirrhosis, the question of CBD stone frequently arises, and that diagnosis can definitely be made or ruled out with a retrograde study (Fig. 7). An extremely narrow biliary tree may be seen in sclerosing cholangitis (32).

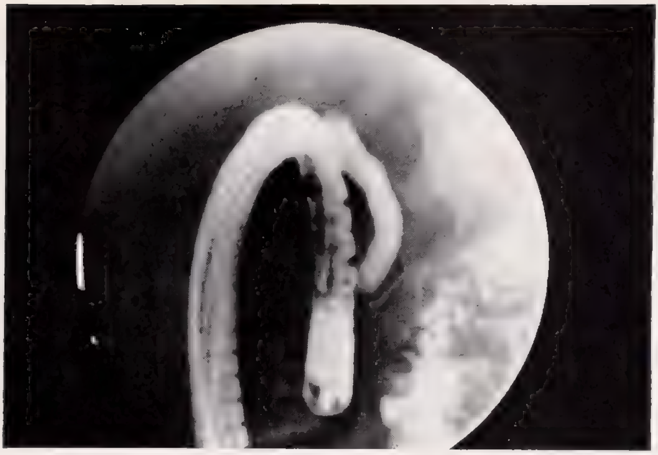

Fig. 5. Abrupt cessation of dye column in common bile duct due to carcinoma. The cutoff is irregular. The pancreatic duct is visualized.

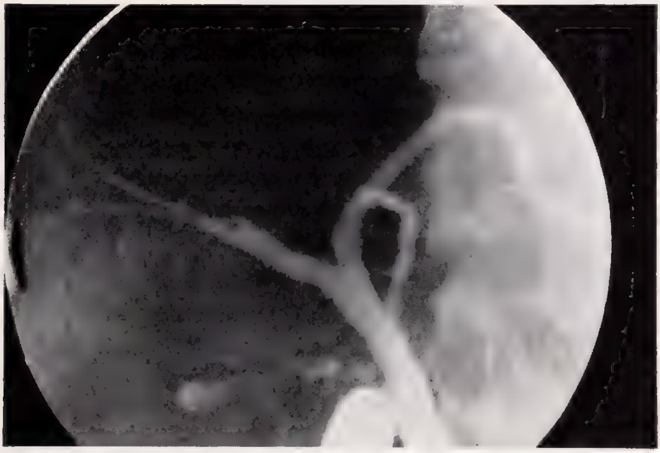

Fig. 6. Normal retrograde cholangiogram in 50-year-old man with jaundice and liver function tests typical of obstruction. Following this ERCP, exploratory laparotomy was cancelled and a liver biopsy showed typical changes of intrahepatic cholestasis.

The gall bladder is frequently filled and stones may be seen. Patients who develop pain after cholecystectomy may have a diagnosis of "cystic duct stump syndrome" made, and filling of the stump may be faint on intravenous cholangiogram. Retrograde study may demonstrate, as illustrated in Figure 8, a normal cystic duct stump. Other biliary tree problems may not be elucidated by routine oral or intravenous contrast studies, and Figure 9 demonstrates a filling defect in the neck of the gallbladder in a patient with recurrent right upper quadrant pain. Surgery revealed this to be a submucosal stone. Biliary-intestinal anastomoses are easily visualized and opacified through the surgically produced intestinal orifice (Fig. 10) (33).

By judicious positioning of the patient, an intrahepatic cholangiogram may

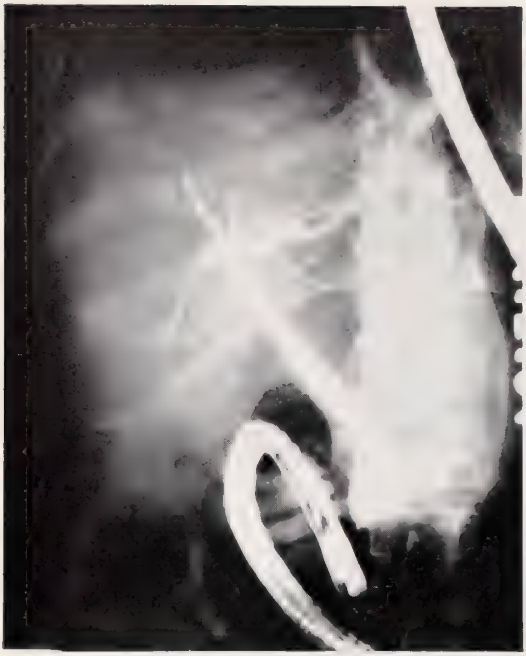

Fig. 7. Normal cholangiogram in patient with primary biliary cirrhosis. Patient had previous cholecystectomy, and because of pain and jaundice was scheduled for exploratory laparotomy prior to this study.

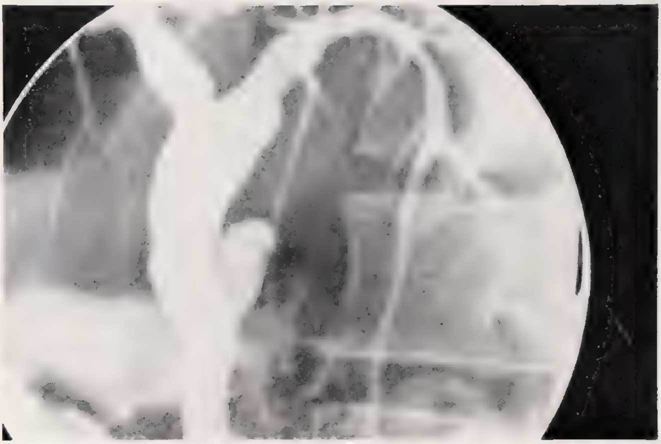

Fig. 8. Postcholecystectomy, this patient had persistent right upper quadrant pain. Intravenous cholangiogram faintly demonstrated a prominent cystic duct stump but the presence of a stone in the stump could not be ruled out until this study revealed a large, but normal stump.

be seen, with diagnostic information provided about hepatic abscess, hepatic infiltrative processes, carcinoma, ductal dilation and even cirrhosis (34). Failure of cannulation cannot be taken as evidence of disease of the ductal system since a significant rate of failure occurs in the presence of normal ducts.

Endoscopic pancreatography The normal PD is widest in the pancreatic head (3.3 to 4.8 mm in diameter) (25, 35–40) and tapers toward the body (3, 13,

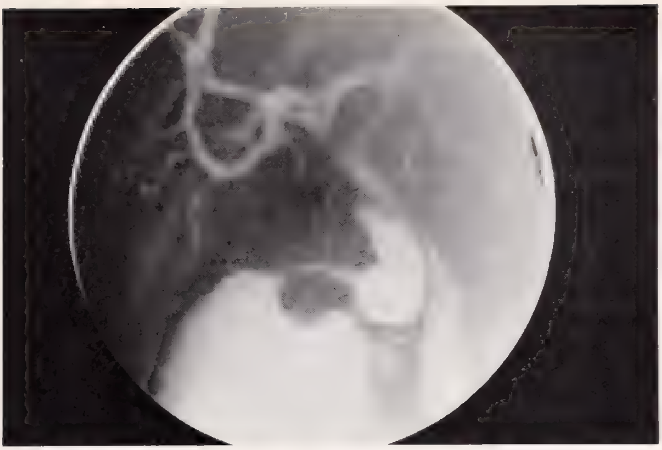

Fig. 9. Round defect in the neck of the gallbladder in young woman with right upper quadrant pain and completely normal tests including oral cholecystogram and intravenous cholangiogram. Exploratory laparotomy revealed the filling defect to be an impacted submucosal stone. All symptoms cleared after cholecystectomy.

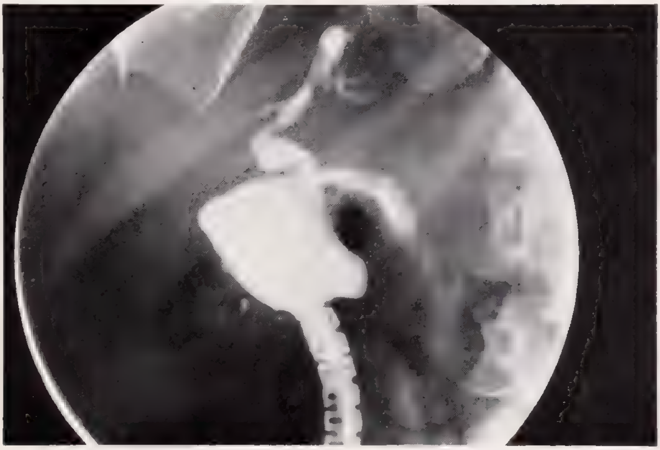

Fig. 10. Endoscope in duodenal bulb. The catheter was inserted directly into the midportion of the common duct through the choledocho-duodenal anastomosis. The intrahepatic portion is filled above the opacified duodenal bulb and the distal common duct is seen medial to it. No stones or obstructions are seen in the biliary tree.

41–45) (2.7 to 3.4 mm) and tail (1.6 to 2.3 mm) in a smooth fashion (Fig. 11). The duct tends to be wider in older patients (3).

The configuration of the Japanese PD (3) is most frequently of a smooth ascent from origin to left upper quadrant (48.5 percent), and less often rises slightly, then plateaus horizontally (26.5 percent), while some ascend to the left upper quadrant in a zigzag pattern (16.2 percent), and only a few (8.8 percent) descend slightly. In my experience, the American PD is more often horizontal, and frequently descends toward the left iliac crest. The duct of Santorini is only seen in 32 percent of normal pancreatograms (Fig. 12) (3). Distension

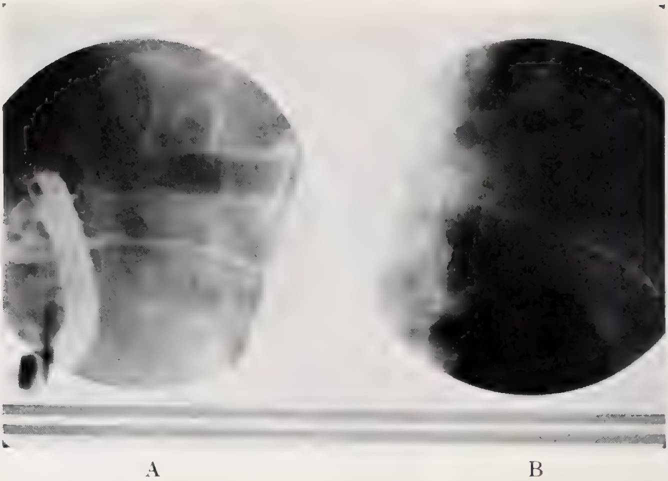

FIG. 11A & B. Smooth tapering of pancreatic duct toward the tail. Note the fine secondary branches perpendicular to the main duct. The duct descends toward the left iliac crest.

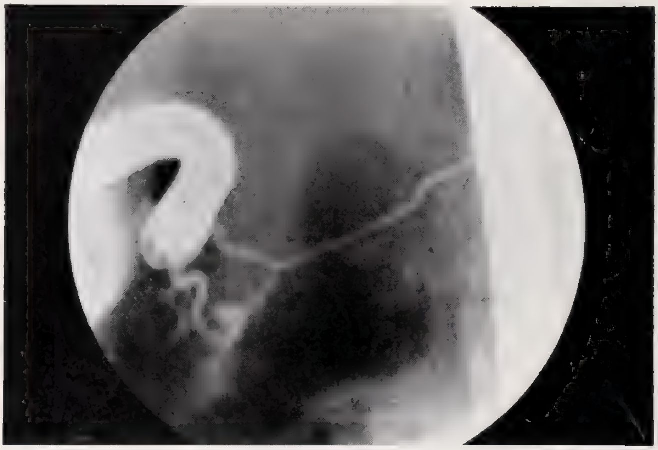

FIG. 12. Main pancreatic duct (Wirsung) is tortuous and courses downward prior to ascending. The duct of Santorini is filled retrograde and meets the duodenum several centimeters proximally.

of the PD with contrast will result in filling of secondary PD branches in about one quarter of pancreatograms; more filling may cause dye to flow into the acini, with a characteristic whitish "fluffy" appearance. The safety of acinar filling has been questioned (2). The normal pancreatic duct empties completely in 5 minutes creating a need for haste in performance of x-ray studies (2). The PD empties slightly slower in the aged patients (3).

In the presence of pancreatic carcinoma arising in the parenchyma, the PD may appear completely normal (28), but some investigators have found ductular abnormalities in all cases (35, 46). Various configurations of the PD have been

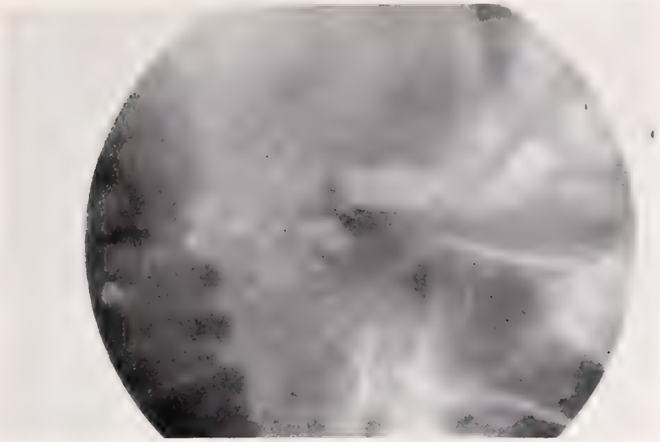

Fig. 13. Carcinoma of the pancreas with lack of filling of the proximal pancreatic duct due to tumor and dilation of the distal duct behind the tumor. The duodenum is not affected as demonstrated by the normal contour on air study.

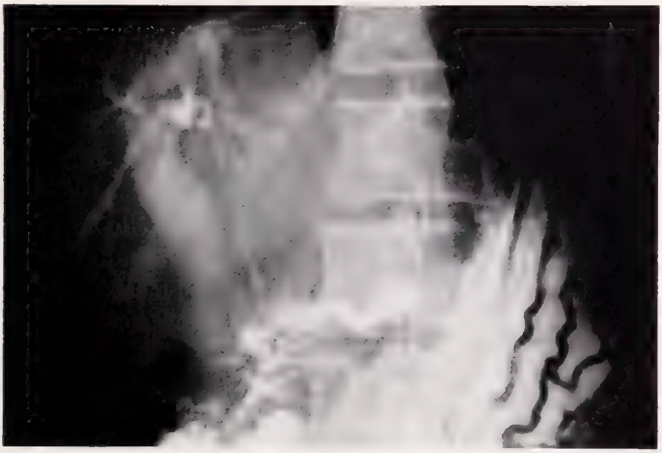

Fig. 14. Dilated common duct in patient with markedly dilated pancreatic duct. Contrast media is in the stomach.

described in carcinoma (Fig. 13), and it may appear as obstruction to the flow of contrast media, as a stenotic segment of variable length, or as a defect in the acinar filling of an opacified gland (28, 35). False positive diagnoses occur, and an apparent block in the pancreatic duct may be due to causes other than cancer, such as nonfilling of a pseudocyst or incomplete filling of the PD. Discovery of pancreatic cancer by ERCP is not a useful screening test, for the rates of survival following resection of those found by pancreatography have been low (47).

Prior to surgery of the pancreas, especially in chronic pancreatitis, demonstration of pancreatic pathologic anatomy (location of strictures or cysts) may assist the surgeon in planning the procedure. Figure 14 illustrates a dilated PD in chronic pancreatitis with the dilated CBD faintly visualized. Figure 15 is a

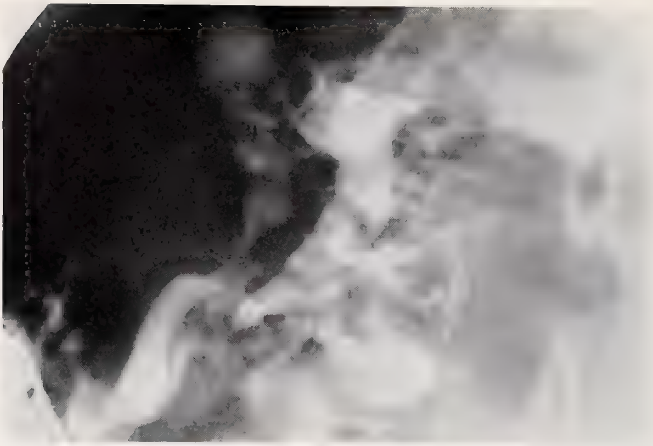

FIG. 15. Close-up of proximal ducts shown in previous figure. The distal portion of ducts in the lower left corner are normal. Both ducts become markedly narrowed by the pancreatic inflammatory process, and then are dilated proximal to the strictures. Note the sacculation (pseudocyst) in communication with the dilated pancreatic duct.

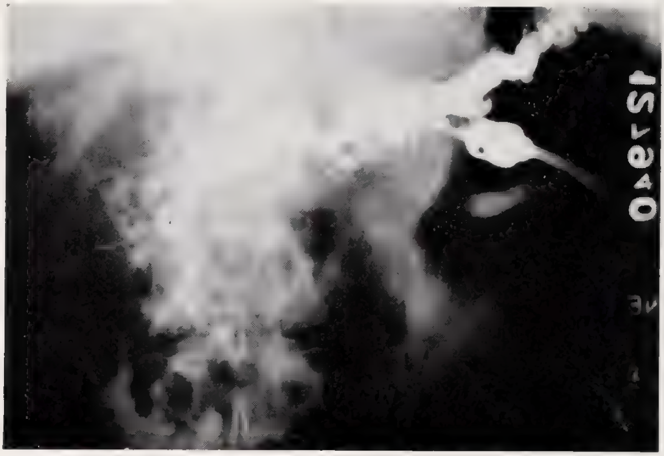

FIG. 16. Operative pancreatogram of patient demonstrated in Figures 14 and 15. The stricture in the lower left of the picture is not well demonstrated, and without the previous ERCP, could not have been correctly interpreted. The dilated common duct is not visible on this study.

close-up of the narrowed CBD adjacent to narrowed PD. Figure 16 is the operative pancreatogram on the same patient, demonstrating much less information about the PD than was acquired via the ERCP, and showing no visualization of the CBD. Operative pancreatograms are limited by the technique and the inability to move the patient's position.

Pseudocysts may cause PD obstruction and be confused with carcinoma, as seen in Figure 17. Because the clinical impression in this patient weighed heavily in favor of a benign condition, a repeat ERCP in 3 months revealed filling of the

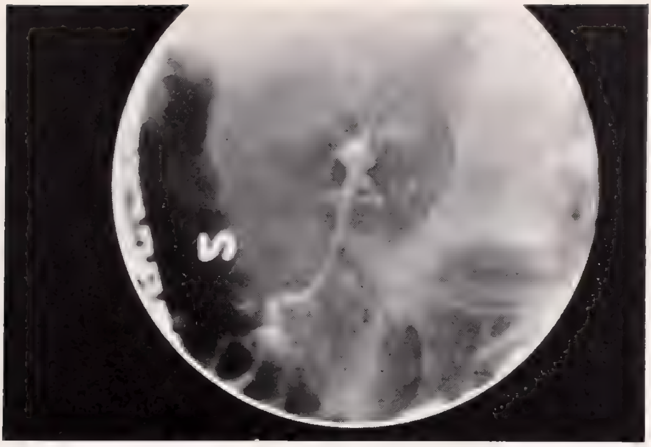

FIG. 17. Complete retrograde obstruction to flow of contrast material in pancreatic duct. Because of clinical impression that this patient had pancreatic inflammatory disease rather than carcinoma, exploratory laparotomy was not performed.

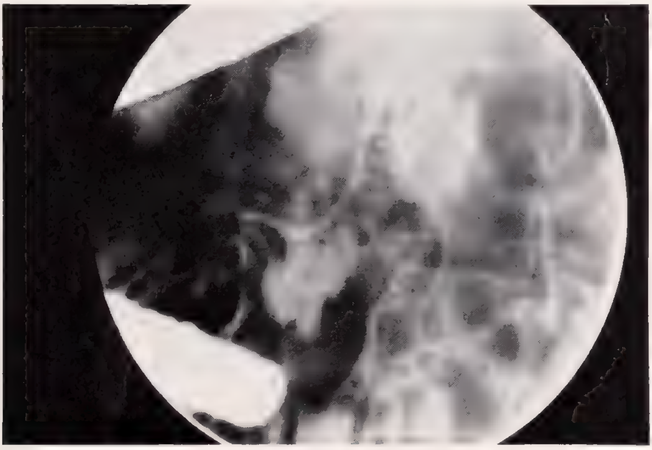

FIG. 18. Same patient as shown in Figure 17, three months later. The patient felt well, but a large pseudocyst was filled.

cyst (Fig. 18). Hemorrhage from a pancreatic pseudocyst has been diagnosed by ERCP (48).

Filling of the lateral ductular branches off the main PD usually reveals them to be small and filamentous, but those in chronic pancreatitis are blunted and thick. Minimal clinical pancreatitis may reveal minimal ductular changes, but both clinical and biochemical parameters of pancreatitis may exist in the presence of a normal PD (2, 28). Pancreatic ductular ectasia is a late finding in advanced chronic pancreatitis, and severe parenchymal insufficiency may be present without affecting the ductal system (40, 49). The differential diagnosis between a dilated duct secondary to pancreatitis or due to carcinoma may be difficult (50).

Complications and Limitations

Inflammatory pancreatitis is the complication with which investigators are most concerned. Troublesome acute pancreatitis has been infrequently encountered, and only one case of necrotizing pancreatitis has been reported (51). A rise in serum amylase after pancreatography is seen in 20 percent (28), 33 percent (31), 52 percent (36) of cases with normal pancreatic ducts but is usually not accompanied by a clinical inflammatory response. Patients frequently complain of abdominal pain during distention of the pancreatic duct, but I have never encountered an instance of clinical pancreatitis with persistent pain, fever and abdominal tenderness following ERCP. Those cases of clinical pancreatitis which have been reported responded promptly to routine therapeutic measures. The level of amylase elevation has been correlated with the degree of opacification of the pancreatic ducts and glands (3), and actual pancreatitis may be induced by a combination of overdistension of the PD (52) and by the pressure with which contrast media is injected (51, 53–55). Devices (28, 56, 57) have been developed to regulate the rate and pressure of the intraductal injection. Trasylol® has been used (2, 3, 16) in an attempt to reduce the incidence of pancreatitis, but it does not appear to be helpful. The presence of acute pancreatitis may present a contraindication to ERCP. Infectious complications usually follow injection of contrast media beyond a stricture with secondary retention of dye due to insufficient drainage. Although antibiotic therapy may be of benefit, the best approach is surgery (28) once a stricture with proximal retention of dye is visualized. Antibiotics may be mixed with contrast media to achieve both opacification and prevention of infection. Sterilization of the cannula does not seem practical since it is passed through the instrument and duodenum, both of which are nonsterile, prior to entering the papilla.

No allergic reactions during ERCP have been reported to any of the radiographic contrast media, perhaps because the contrast is injected into a duct and not into the blood stream.

Contamination of the endoscope by bacteria or viruses may occur, although no cases of hepatitis have been reported secondary to endoscopy (58). Disinfection may be adequate with ethylene oxide or with a glutaraldehyde solution (4, 58, 59) although most endoscopy units rely on rinsing the outer sheath and inner channels with a detergent or iodine-solution and alcohol. Because of the theoretic possibility of hepatitis transmission, a patient with a positive hepatitis-associated antigen test may present a relative or absolute contraindication to ERCP (4).

The technique of ERCP is difficult and time-consuming. Several interesting articles and comments have been written as to the cost factors involved versus the benefits accrued (60–63). The success of the procedure depends on the integrated function of an expert endoscopist, an able assistant and a radiologist as well as expensive x-ray equipment with image intensification. In spite of these factors, the ability to make a definitive diagnosis in cases where exploratory surgery was previously required results in great benefit to the patient. With training, the procedure becomes less formidable, and neophytes may even train on a canine papilla (10).

Conclusions

Endoscopic retrograde cholangiopancreatography has been shown to be a feasible technique with a low incidence of complication, and a success rate of 80 to 90 percent. The biliary tree can be opacified in spite of the level of icterus or the state of hepatic function. The need for "blind" percutaneous puncture of the hepatic capsule with the risk of bleeding or bile leakage has diminished because of this procedure. The side effects are minimal and the benefits to the patient are large.

Pancreatography has made evaluation of the entire pancreatic duct possible in the intact human. The diagnosis of chronic pancreatitis can be substantiated, and, if surgery is contemplated, the exact location of strictures and pseudocysts may be demonstrated. Better methods must be developed for detection of pancreatic carcinoma, and the addition of cytological studies (64, 65) may be rewarding.

Pure pancreatic juice can be obtained (in large quantities under maximal secretory stimulus) (66) for physiologic studies. Endoscopic papillotomy and removal of stones in the common duct is an exciting advance.

The technique is difficult and time-consuming, but represents a distinct advance in the diagnosis of pancreatic and biliary tract diseases.

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The Current Status of Esophagoscopy, Gastroscopy, and Duodenoscopy*

JEROME D. WAYE, M.D.

Esophago-Gastro-Duodenoscopy

Upper intestinal panendoscopy is a well-established diagnostic modality. The patient acceptance is excellent, the morbidity of the procedure is extremely low, and the amount of information which can be gained is great. The entire esophagus can be inspected from the cricopharyngus muscle to the cardioesophageal junction. The mucosal junction at the distal esophagus can be distinctly seen, and a diagnosis of hiatus hernia can be made endoscopically. Many lesions seen may be safely biopsied, and strictures and mucosal rings may be identified and dilated.

The stomach no longer contains "blind spots" for the endoscopist and no areas of gastric mucosa are immune to direct visualization with the newer fiberoptic instruments. Instruments currently being manufactured have the capability of tip deflection in a tight bend so that the lens of the instrument placed in the stomach can actually demonstrate the cardioesophageal junction and view the shaft of the instrument passing through the cardia. Still photographs, movies, and television photography are easily accomplished within the lumen of the gastrointestinal tract. The pylorus is always visible and the fiberscope can be passed through the antrum into the pyloric canal under direct vision.

The duodenal bulb may be directly visualized and evaluated. The normal bulb is devoid of fold patterns and distends symmetrically where the bulb with chronic ulcer disease or acute peptic pathology may be seen as contracted and deformed. Ulcers, tumors, and Brunner gland hypertrophy are easily recognized. The entire duodenal sweep can be inspected and biopsied. The upper jejunum has been invaded endoscopically and I have even biopsied a jejunal carcinoma located 50 cm beyond the ligament of Treitz (*Fig. 1*). An instrument has been devised (1) similar to a Cantor tube with tiny fiberoptic light and visual bundles. This can be passed to the ileocecal valve and slowly withdrawn to give a complete view of the entire small bowel, a rewarding diagnostic modality in cases of occult gastrointestinal bleeding. Diagnostic as well as therapeutic endoscopy will be discussed in this article, directed toward acquainting the general physician with the newest capabilities of fiberoptic instruments.

Instrumentation

Separate instruments for examination of the esophagus, stomach, and duodenum are no longer necessary. The newer panendoscopes permit one-instru-

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* Figures in italics denote color photographs. All color for this article is on page 65.

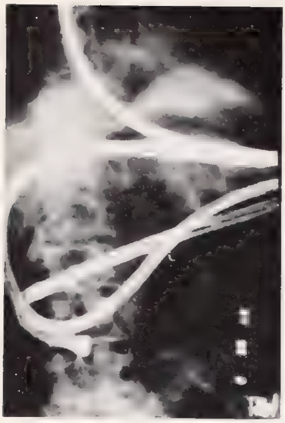


FIG. 1. Tip of endoscope located 20 inches below the ligament of Treitz. A biopsy of carcinoma was obtained at this site from a smooth tumor seen on upper gastrointestinal x-ray. The instrument was a prototype supplied by the Olympus Corporation of America.

ment visualization of all upper intestinal structures. For diagnostic endoscopy the rigid-tube esophagoscope has very little advantage to recommend its use. The advent of flexible endoscopes has rendered unnecessary the requirement of the "correct position" of the patient, supine with neck hyperextended, and no longer is there need of an assistant to hold the head to align the instrument along the esophagus. The Eder-Hufford esophagoscope with a flexible obturator and a rigid metal portion is passed with the patient in the left lateral position but still requires a "head-holder" because the position of the pharynx and cricopharynx plays a substantial role in directing the angle of the tip of the rigid instrument. The Eder-Hufford rigid esophagoscope has a telescopic lens attached to its proximal end, affording a 4-fold enlargement of the mucosa at the distal end of the instrument. Otolaryngologists currently use a similar rigid tube and pass it without a flexible obturator under direct vision into the upper esophagus. Otolaryngologists tend to pride themselves on not "needing" a magnification lens, and are able to visualize a small round spot of mucosa seen through the 1.0 cm diameter instrument, from a distance of 50 cm.

The rigid and "semi-flexible" metal esophagoscopes are useful in the removal of foreign bodies in the esophagus, since large biopsy-grasping forceps may be passed down the hollow lumen to permit intra-esophageal manipulation. Several recent reports (2, 3, 4) indicate, however, that many foreign bodies may be removed with various grasping snare devices using the flexible endoscopes. Bougie-dilatation of esophageal strictures is easier under direct vision with rigid endoscopes than via the flexible systems.

In reference to semi-flexible or rigid gastroscopes, mention will be made because of historical interest. Prior to the age of controllable flexibility introduced by glass-fiber technology, the image was transmitted along the semi-flexible gastroscopes by a series of prisms and lenses. With the prism gastroscope, a deflection of the flexible portion greater than 20–30° from the horizontal caused aberrations of the visual image. The patient assumed a position on the left side similar to that used for semi-flexible esophagoscopy. The preparation always required meticulous local anesthetization of the posterior pharynx to prevent discomfort. Because the flexible portion was the distal half, the proximal half of these gastroscopes was rigid metal, and adequate protection of the incisor teeth was mandatory to prevent their accidental dislodgement. Vision was excellent through these lens-optical systems, and was directed laterally. Biopsies were not possible with the standard instruments but larger caliber "operating" gastroscopes were available for special cases.

The fiberoptic panendoscopes currently in use afford a 12-fold magnification of the image as seen at the tip of the instrument. Air must be insufflated into the gut lumen to distend the walls for visualization because, unlike the hollow-tube esophagoscopes, atmospheric pressure does not enter the solid fiberoptic panendoscope to permit equilibration of pressure.

The angle of vision of the forward viewing panendoscopes varies from 60° to 75°, and that angle of vision is effectively extended by the ability to deflect the tip in multiple combinations of up and down and right and left angulations with controls on the proximal end of the instrument. Fluid, mucus, and blood can be aspirated through the instruments via suction/biopsy channel. Water can be injected through the instrument to clean accumulated debris from its tip. The two major firms which manufacture instruments used in the United States of America are American Cystoscope Makers, Inc. (ACMI) and Olympus Corporation of America. Machida Endoscope Company has developed an instrument that is capable both of forward and lateral vision by deflection of a prism within the distal tip portion. This has several very distinct advantages, but Machida Instrument Company is only beginning to become established in the United States.

The first fiberoptic gastroduodenoscope (manufactured by ACMI) was introduced in the United States by Dr. Basil Hirschowitz in 1962 (5). This instrument was a lateral viewing instrument with an incandescent bulb in its distal end and a variable focus requiring continual adjustment. The tip could not be manipulated, but the instrument was flexible. A separate esophagoscope was manufactured with the distal lens at the tip of the instrument providing the forward vision needed to view the esophageal lumen (6, 7). Developments came rapidly and the original "gastro-camera," developed in Japan, which could be swallowed and through a series of elaborate manipulations took photographs (but provided no visualization) of every aspect of the gastric mucosa (8), has been replaced by a proliferating field of newer panendoscopes with direct-vision capability. Instruments have become smaller in diameter and more flexible. The smallest instrument currently in use is a 6.8 mm (Fig. 2) direct end-on viewing instrument capable of visualizing the esophagus, stomach, and duodenum. Currently the most widely used instruments are fairly durable and measure approximately 1.2 cm in diameter, and have direct forward vision (Figs. 3 and 4). Some physicians (9, 10) have advocated a lateral viewing instrument (Fig. 5) to examine the fornices of the duodenal bulb which cannot be seen with the direct forward viewing instruments in spite of the wide-angle lens. Since the direct forward viewing instrument permits a tangential view of the walls of the lumen, flat lesions may tend to be overlooked with the direct

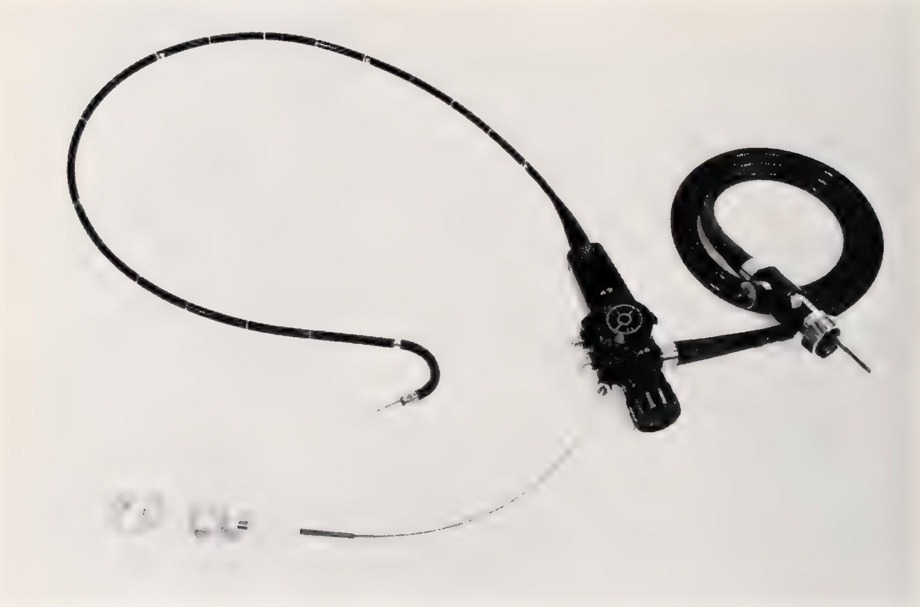


FIG. 2. Olympus GIF-P panendoscope. Diameter is 6.8 mm. Dial on head permits deflection of tip 300° in one plane. Biopsy forceps are in place through the suction/biopsy channel.

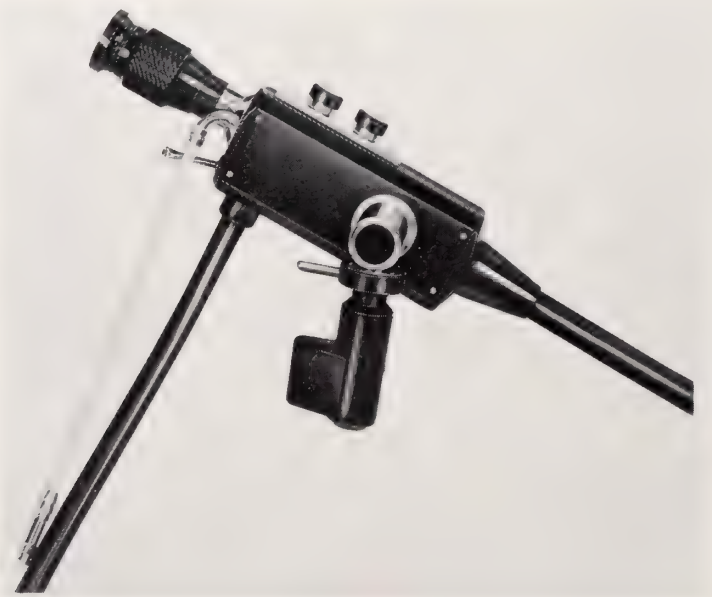


FIG. 3. Proximal head of ACMI forward-viewing panendoscope. A single stick mechanism provides polydirectional rotation of the distal tip.

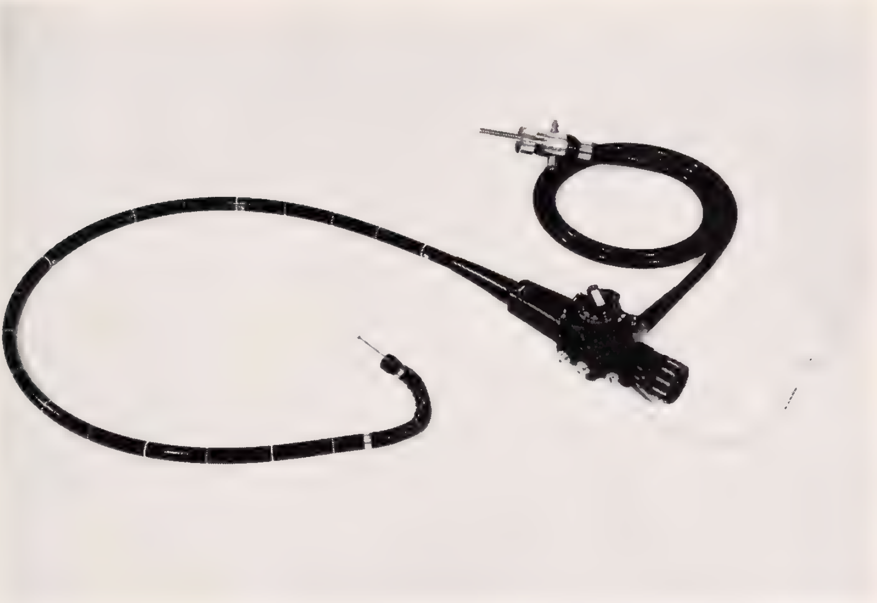


FIG. 4. Olympus GIF-D2 forward viewing panendoscope. Full range of tip motion is obtained by rotation of dials on instrument head. The diameter is 1.2 cm. Biopsy forceps are in place.

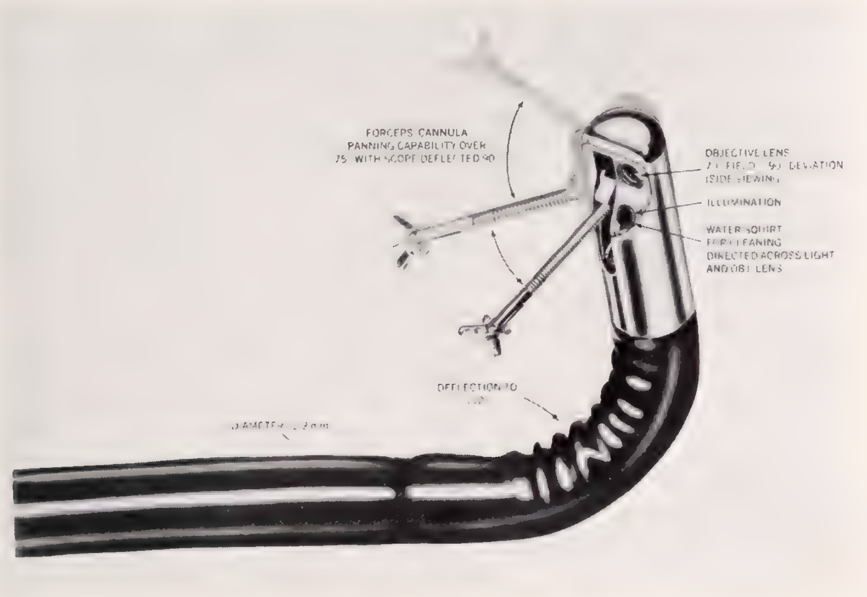

FORCEPS CANNULA
PANNING CAPABILITY OVER
75 WITH SCOPE DEFLECTED 90
OBJECTIVE LENS
FIELD 90 DEVIATION
(SIDE VIEWING)
ILLUMINATION
WATER SQUIRT
FOR CLEANING
DIRECTED ACROSS LIGHT
AND OBJ LENS
DEFLECTION TO
DIAMETER

FIG. 5. Distal tip of ACMI lateral viewing gastroduodenoscope. The visual field is directed at 90° to the long axis of the instrument to permit direct face-on view (rather than tangential) of the walls of the stomach and duodenum.

forward-viewing instruments, and small lesions may be obscured by overhanging folds. To overcome this disadvantage, the Machida Instrument Company (of Japan) has developed a panendoscope permitting both forward and lateral viewing with manipulation of a prism in the distal end. The angle of vision of this system is narrower than the standard instruments. The Machida Instrument Company has only recently begun to distribute its instruments within the United States. A partial answer to this problem has been met by the Olympus Corporation of America who recently introduced a forward viewing panendoscope with a 30-degree oblique angulation of the distal lens system permitting a somewhat greater lateral visualization than was achieved with the direct forward viewing instrument.

ACMI has manufactured an operating gastroscope (11), with a slightly narrower visual bundle but with two suction/biopsy/operating channels permitting use of suction at the same time that an operative instrument is used, or insertion of two operative instruments through the endoscope simultaneously. Every year new modifications are being introduced and there is no end to the eventual capabilities of the instruments.

Indications

Gastrointestinal bleeding is a major reason for performing upper intestinal endoscopy. Endoscopy can be performed at the bedside, in the emergency room, or in the intensive care unit with a minimum of preparation. The exact bleeding site can be found in over 95 percent of patients and a course of treatment can be immediately outlined based on an immediate definitive diagnosis. Roentgenographic examination of the upper gastrointestinal tract in the critically ill patient is being replaced by emergency intestinal panendoscopy. Barium esophagram will fail to demonstrate esophageal varices in a substantial portion of patients with varices (12, 13, 14). Patients with marginal ulcers in a postoperative stomach may not have the ulcer demonstrated on a barium study *(Figs. 6 and 7)*. A patient with esophageal varices and upper gastrointestinal bleeding, frequently has other sources of bleeding, such as peptic ulcers or gastritis and only direct visualization will permit accurate localization (15–18). Rational management of the bleeding patient depends completely on making the correct diagnosis.

Another major indication for upper intestinal endoscopy is the finding of a pathological lesion on radiographic examination. A filling defect in the esophagus can be directly seen and biopsied. Washings or brushings can be obtained for cytologic study, and a definitive diagnosis may be made as to whether the lesion is mucosal or submucosal. If carcinoma is found, a tissue diagnosis is possible to make the differential diagnosis between adenocarcinoma or squamous cell carcinoma. Hiatus hernias can be seen directly and any evidence of bleeding or gastritis within the hernial sac is readily evident. Within the stomach, current biopsy techniques permit the histologic differentiation between benign and malignant gastric ulcers. If carcinoma is found on biopsy, the necessity to treat the patient intensively over a 2–3 week period to ascertain if healing develops can be obviated and surgery performed directly.

A third indication for upper intestinal endoscopy is symptomatology unexplained by x-ray findings. Patients may complain of epigastric discomfort, "burning" in the epigastrium and dyspepsia and have a normal stomach x-ray, but gastritis may be playing a role and its presence can be proven by biopsy. Duodenitis is being reestablished as a diagnostic entity since erythema, edema and minute superficial ulcers and erosions in the duodenum can be easily identified endoscopically, but because no specific ulceration is present, a "negative" upper gastrointestinal x-ray series may be seen.

Among the therapeutic applications of upper intestinal endoscopy are: 1. Rupture of mucosal rings in the esophagus (19); 2. Removal of foreign bodies in the esophagus and stomach (2–4); 3. The ability to stop gastrointestinal bleeding by application of electrocoagulation current (20, 21), by direct instillation of a vaso-constrictive agent such as levophed or epinephrine or by the application of a clip to a bleeding vessel (22). Gallstones impacted at the ampulla of Vater have been successfully removed with the endoscope (23). Physiologists may be delighted by our ability to collect pure pancreatic juice by placing a catheter into the pancreatic duct under direct visualization.

The major contraindication to upper intestinal endoscopy is the uncooperative patient. The sheath of the fiberoptic instrument is necessarily supple to permit the flexibility necessary for adequate endoscopy. A patient may bite the endoscope and cause damage of several hundred dollars if the outer sheath is punctured, or $1000.00 to $1500.00 damage if the sheath is punctured and several of the optic fibers are broken.

Preparation of the Patient

In the unobstructed patient it is only necessary to keep the patient fasting from midnight prior to the examination until the procedure is performed. This is adequate to provide an empty stomach with minimal secretions at the time of the endoscopy. If the patient has achalasia or esophageal stricture, it may be necessary to keep the patient on liquids for the lunch and supper preceding the endoscopic examination and then nothing by mouth following supper. In the unobstructed patient, it is no longer necessary to pass a gastric emptying tube into the stomach prior to endoscopy since the pool of secretions is usually minimal and can be suctioned out during the procedure (24).

The hospitalized patient should be visited prior to endoscopic procedure, and given an explanation of the nature of the examination. The apprehension of most patients can usually be diminished by a few reassuring words and by some knowledge of the procedure. I have noted that the major concern of most patients is that they will not be able to "swallow" the instrument and many tell me that they "gag" whenever anything is in their pharynx. The patient should be made aware that they will, contrary to their desires, not be completely "asleep" during the examination but rather will be sedated to such an extent

Fig. 6. View of afferent and efferent limbs of gastroenterostomy. The afferent limb can be distinguished by the presence of bile.

Fig. 7. Ulcer at the gastroenterostomy site with a yellowish base, almost as large as the stoma. This ulcer was not demonstrated on barium meal x-ray. Spasm secondary to inflammation is responsible for the stomal narrowing. The small bowel is visible through the stoma.

Fig. 8. U-turn view of instrument (black with a white transverse marker) passing through the esophagus into stomach. The tip is at the level of the angulus and bent up to obtain this picture. Red area to left of scope is a fundal cancer.

Fig. 10. Circumferential ring at the mucosal junction. Reddish color seen through the ring is gastric mucosa, with folds pointing to the closed hiatal rosette at the 3 o'clock position.

Fig. 12. Thick, muscular-appearing ring during contraction (same patient as Figure 11). Through the ring the phrenic ampulla may be seen in a collapsed phase.

Fig. 13. Umbilicated lesion at 11 o'clock. This lesion was discovered on x-ray and proved to be a pancreatic rest. Note radiation of folds to the area.

Fig. 15. Same patient as Figure 14. Typical benign, smooth ulcer with surrounding erythema and folds radiating to the ulcer edge. The base is yellowish and there is no mass around the ulcer.

Fig. 17. Irregular stellate ulcer with multiple areas of involvement. No mass was seen endoscopically, and all biopsies were benign. This ulcer healed completely with no radiographic or endoscopic abnormalities.

Fig. 18. Small ulcerated carcinoma not visible on gastrointestinal x-ray. Note the bulge just below the ulcer, indicating the presence of a mass expanding the submucosal tissues. The base of the ulcer is clean and yellowish, and its appearance does not aid in the differential diagnosis between benign and malignant ulcers. Biopsies must be directed to the edge of the ulcer.

Fig. 19. Extensive gastric malignancy with nodularity and encroachment of the lumen. Biopsy revealed carcinoma.

Fig. 20. Area of friability in the gastric cardia found during investigation of chronic blood-loss anemia with negative gastrointestinal x-rays. Biopsies showed superficial carcinoma.

Fig. 21. Superficial gastric erosion (yellowish base) in the prepyloric area. Pylorus is at 6 o'clock. Patient had continuing symptoms of epigastric pains with negative x-rays. Note the erosion is rimmed with a zone of erythema.

Fig. 22. Ulcer on the anterior wall of the duodenal bulb. The dark area is a clot partially covering the yellowish base. To the right of the ulcer are seen the valvulae conniventes of the descending duodenum.

Fig. 23. Tear of Schatzki ring after passage of flexible fiberscope. No significant bleeding occurs following forceful dilatations.

Fig. 25. Tiny esophageal orifice as seen in Figure 24. This stricture cannot be forcefully dilated with the fiberoptic instruments.

Fig. 26. Stricture of esophagus with lumen at 10 o'clock. Red streaks at 12–3 o'clock represent peptic esophagitis.

Fig. 27. Multiple small gastric polyps. These are not amenable to endoscopic removal.

Fig. 29. Solitary polyp in patient whose x-ray was Figure 28. A small erosion at the surface caused bleeding. Because multiple medical factors did not permit surgery, this was resected endoscopically. See Figure 30.

Fig. 30. Polypectomy site on the anterior wall of the antrum immediately after removal. Note lack of bleeding. A portion of the pylorus can be seen behind the pedicle. Histology revealed this to be a benign adenomatous polyp.

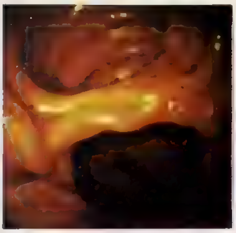
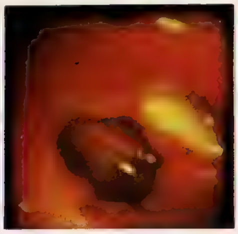


Fig. 6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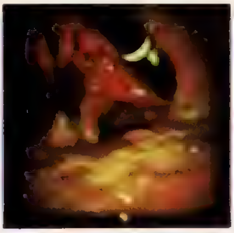
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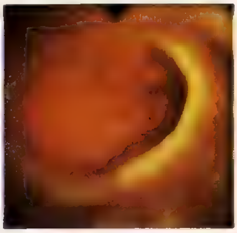
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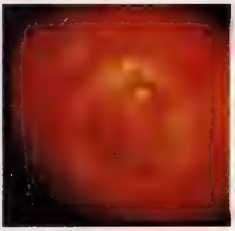
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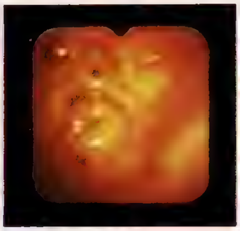
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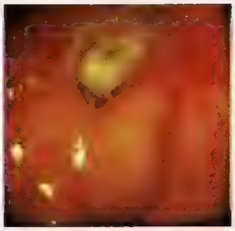
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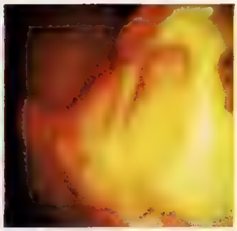
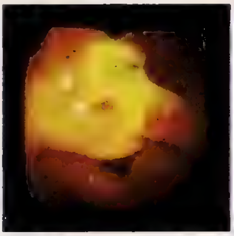


Fig. 17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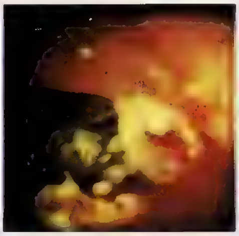
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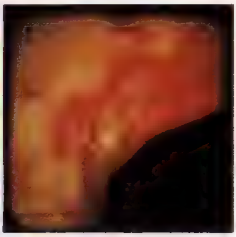
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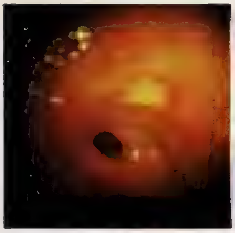
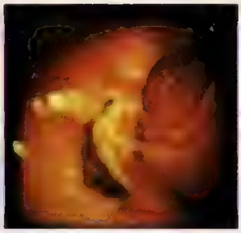


Fig. 21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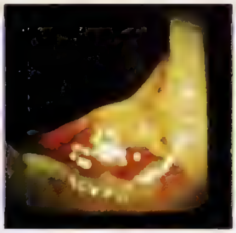
Fig. 23

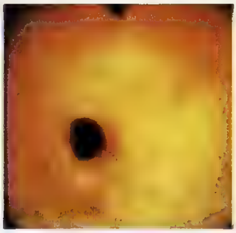
Fig. 25

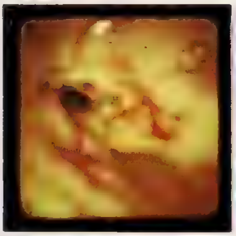
Fig. 26

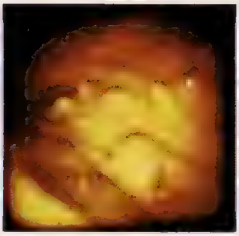
Fig. 27

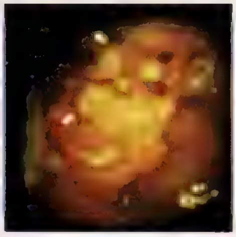
Fig. 29

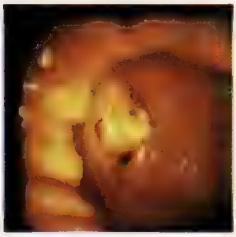
Fig. 30

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that they will not be uncomfortable and that medication will be given to diminish the tendency to gag and retch.

It is quite feasible to perform endoscopic examinations on ambulatory patients, and many patients have upper intestinal endoscopy as an office procedure.

In the acutely ill patient with upper gastrointestinal bleeding, the preparation is vigorous, and a large bore tube is placed in the stomach and several liters of ice water are used for gastric lavage. This not only clears the stomach of clots, but seems to temporarily alter mucosal blood flow to stop or considerably diminish active bleeding at the time of the endoscopy (25, 26).

Medication

A combination of meperidine and diazepam affords excellent pre-endoscopic medication and has multiple effects causing somnolence, diminution of the gag reflex and renders the patient somewhat amnesic for the procedure. Meperidine may be given intramuscularly (50 mg) one hour before the procedure, or immediately intravenously prior to endoscopy. A "butterfly" or scalp-vein needle is placed into the right forearm of the patient to inject preendoscopic medication and allow further drug usage during the examination if it is desired. Following injection of meperidine, a small amount of saline is injected through the plastic tubing and then 5–15 mg diazepam are given, again flushed with saline to prevent development of chemical phlebitis. The dose of diazepam is individualized, but in general elderly patients are well sedated with 5 to 7.5 mg and larger doses are required for husky younger patients. Local pharyngeal anesthesia is no longer used at The Mount Sinai Hospital, and I have not found it necessary in the past 5000 upper intestinal endoscopies I have performed. Patients tolerate introduction of the scope extremely well (27), and the complications of local anesthetics are completely avoided. During the 1974 meeting of the American Society for Gastrointestinal Endoscopy, the most common complication of upper intestinal endoscopy was said to be related to the use of local pharyngeal anesthesia (28). Occasionally, meperidine is not used, and only 5–15 mg of intravenous diazepam suffice to provide adequate patient relaxation. I have noticed that alcoholic patients may develop a paradoxical reaction to diazepam and become combative, hyperactive and render endoscopy extremely difficult or impossible. For these patients, the addition of intravenous meperidine tends to act as a tranquilizing agent. When emergency endoscopies are performed for acute upper gastrointestinal bleeding I prefer not to use any endoscopic medication, since diazepam and meperidine tend to diminish the protective "gag" response. An active pharyngeal reflex prevents aspiration in the acutely bleeding patient who is reaccumulating blood in the stomach during the examination. Eighty percent of patients tolerate emergency endoscopy well without any medication.

Technique

Ambulatory patients are provided with a gown after removal of their shirt/blouse. Medication is given into the right forearm and the patient is turned onto the left lateral recumbent position facing the examiner. Some endoscopists prefer to pass the instrument while the patient is in the sitting position (29), but moving the well-sedated patient from the sitting to lying position may require a muscular assistant. The head rests on a pillow and the instrument is introduced into the pharynx. The examiner places the left index finger into the posterior pharynx and guides the tip of the instrument along the posterior pharynx to the level of the cricopharynx. The cricopharynx is usually encountered at approximately 15 cm from the incisor teeth. The medicated patient, conscious but drowsy and cooperative, is requested to swallow. The cricopharynx opens and the instrument is passed gently through into the esophagus. Another technique is to pass the instrument into the posterior pharynx without using a finger to guide the tip. The controls at the head of the instrument are manipulated to bend the tip along the posterior pharynx, and when the instrument is seen to reach the cricopharynx the patient may be requested to swallow or the scope may be advanced into the esophagus with gentle pressure. Thus, the entire introduction can be performed under direct vision. When direct vision is used a view can usually be obtained down the pharynx into the area of the vocal cords. The instrument is directed away from the vocal cords, somewhat more posteriorly, and the esophagus is entered. Passage of the instrument through the cricopharynx under direct vision may be accomplished even in the comatose patient since the lumen can be seen at all times. Use of this technique also obviates the previous "blind" passage through the pharynx. The entire operation can be performed with the patient in the left lateral position, but the patient may be turned to the back or onto the right side if a large pool of mucous or blood is present and obscures an underlying lesion. Once the scope is advanced into the body of the stomach, the tip is bent upward (toward the pylorus) and the lesser curvature of the stomach is visualized. Further introduction of the scope permits one to look into the antrum and see the pyloric orifice. Peristaltic contractions can be seen and progress in orderly fashion toward the pylorus. The forward viewing endoscope may then be passed into the pylorus. With the complete circle of the pylorus in view, the endoscope is advanced (by gradually introducing the shaft into the mouth) until the tip of the instrument engages the pyloric ring. Usually, only slight pressure is needed to pass the endoscope through the pylorus. As the duodenal bulb is inflated with air, the bulb can be seen to distend to a greater degree than the remainder of the duodenum. The bulb has no fold pattern and the typical circumferential valvulae conniventes of the small bowel commence at the apex of the duodenal bulb. With the patient in the left lateral position, and the tip of the scope in the duodenal bulb, the instrument can be advanced into the descending duodenum when the controls are flexed in the maximally upward and right direction. Gentle pressure will allow the instrument to pass the superior flexure of the duodenum and enter the descending duodenum. The forward viewing panendoscopes can usually be inserted to the area of the inferior knee of the duodenum. Upon withdrawal of the instrument, the ampulla of Vater may be seen on the left (medial) wall of the duodenum as a small protrusion with a reddened tip. This structure can be identified in approximately 75 percent of duodenoscopies performed with the forward viewing instrument. Even though the ampulla of Vater can be visualized it cannot be intubated with the direct forward instruments because the duct systems are at right angles to the long axis of the duodenum, and cannot be entered. The duodenal bulb may once again be inspected upon withdrawal of the instrument through the area; with adequate air insufflation, the entire duodenal bulb can be visualized with the exception of the fornices of the bulb. It has been suggested that a lateral view instrument provides a higher percentage of visualization of duodenal ulcers, especially those in the fornices of the bulb, and those hidden behind edematous folds within a deformed bulb. A technique that I have found useful in visualizing areas hidden behind folds or deformities in the stomach and duodenum is to pass the closed biopsy forceps out into the lumen of the bowel. The closed forceps are passed beyond the deformity, and the tip of the instrument is then deflected toward the area of deformity. The forceps may then be used as a probe to flatten out proximal folds so that distal areas previously hidden by those folds can be seen. As the instrument is withdrawn from the duodenal bulb the circular muscle of the pylorus may gently encircle the instrument tip and can be pulled 10 to 15 cm proximally into the stomach. This never presents a problem, for the vis-a-tergo of the gut causes the bulb and antrum to recoil immediately into their original positions. As the pylorus springs back to its normal shape, the examiner may find that the tip of the scope has been withdrawn to the area of the body of the stomach. The instrument must then be re-advanced into the antrum so that the area on the gastric side of the pylorus can be adequately inspected. Once the antrum is inspected the instrument can then be withdrawn into the body of the stomach, affording complete inspection of the re-entrant angulus of the stomach and its superior and inferior margins. With the instrument lying on the greater curvature aspect of the stomach (this is the usual curved position of the instrument within the stomach when the patient is in the left lateral position) upward deflection of the tip of the instrument will permit visualization of the cardia and the cardioesophageal junction with a view of the instrument passing through the hiatal orifice (*Fig. 8*). Biopsies may be taken under direct vision at any location within the stomach (30). Further withdrawal of the instrument permits one to visualize the anterior and posterior walls of the stomach as well as greater and lesser curvature. If the angle of vision of the instrument does not permit simultaneous peripheral view of all these walls, the tip of the instrument must be rotated in a circular fashion so that all portions of the walls can be seen during withdrawal. The forward viewing instruments provide a tangential view along the lesser curvature of the stomach. A better view is obtained of the greater curvature aspect since the scope is pointed directly forward toward that curvature and slides along it during advancement into the stomach. A large gentle loop is formed along the greater curvature as the scope is inserted into the pylorus. As the instrument is withdrawn from the mouth, the loop is straightened, and the tip slides along the lesser curvature aspect of the stomach with no slack. Careful attention must be paid to the contours of the lesser curvature upon withdrawal of the instrument lest a small ulcer be hidden behind an edematous ridge, and be missed completely. Any irregularity along the lesser curvature must be carefully inspected. Use of the forceps as a probe may be helpful in this regard. The lateral viewing instruments, still enjoying popularity among some endoscopists, permit excellent visualization of the lesser curvature even though the instrument is advanced along the greater curvature aspect of the stomach. Since the instruments that permit both forward and lateral view with a change in prism direction have too narrow an angle of vision for adequate scanning of the stomach, the Olympus Corporation has introduced a forward-viewing instrument with a slight obliquity to the lens (30 degrees) to permit better visualization of the lesser curvature aspect of the stomach. With the instrument tip near the cardioesophageal junction, the instrument should be fully rotated to obtain good visualization of the cardia in a forward direction even though it has already been seen in a retrograde fashion with the "U-turn" technique. The instrument is then withdrawn through the hiatus and through the esophagus. I achieve better control of the instrument during introduction by using the thumb of the left hand on the up-down control of the instrument while advancing the instrument through the esophagus, stomach and pylorus with the right hand on the shaft of the instrument. Once full introduction has been accomplished, I prefer to place my right hand on the right-left control of the endoscope and the left thumb on the up-down control and remove the instrument by pulling on the head of the scope and "walking away" from the patient, rather than pulling on the shaft of the instrument with the right hand. I believe that this permits an easier circumferential sweeping of the tip of the endoscope so that pathology will more readily be seen. If a pool of mucus is present within the fundus of the stomach, it is located on the greater curvature aspect and suction will completely remove it. During the entire examination, air must be intermittently insufflated to permit adequate visualization. Usually, overdistention induces the patient to belch in order to obtain relief.

Endoscopic Landmarks

The cardioesophageal mucosal junction is usually located in most normal-sized adults at 40 cm from the incisor teeth. The location of this junction is variable and may, in a small person, be at 35 cm. The mucosal junction can readily be recognized in all patients and is represented by an irregular circumferential serpiginous junction between the salmon-pinkish-white color of the esophageal mucosa and the reddish-orange color of the gastric columnar epithelium. Occasionally a ridge may be seen at the junction of the squamous and columnar epithelium (Figs. 9 and *10*). When the esophagus is distended with air the ridge may become prominent, and it will be noted to be circumferential. This is the "B" ring (31) or the "Schatzki" ring. When the diameter of this ring is less than 1.2 cm, it may give rise to symptoms of dysphagia. About 1.5–

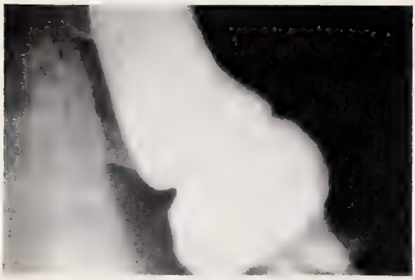

FIG. 9. Schatzki ring is indicated by lateral notches on the x-ray. Since the ring is at the junction of esophageal and gastric mucosa, a hernia is present above the diaphragm.

2.0 cm above the mucosal junction a fixed contractile ring may be seen that does not propagate down the esophagus. This is the "A" level contractile ring (32) which may appear to be a rosette (the "A-level" rosette) and marks the superior portion of the phrenic ampulla (Figs. 11 and *12*). In a normal patient, another esophageal rosette will be seen as the esophagus narrows to pass through the diaphragm; this is the "hiatal rosette." Normally, the mucosal junction is located at the level of the hiatal rosette. Because the squamo-columnar junction is circumferential and perpendicular to the long axis of the esophagus, and because the diaphragm tends to slope downward as it passes posteriorly, an edge of the squamo-columnar junction may be visible endoscopically on the posterior wall of the contracted esophagus at the hiatal rosette. When the entire circumference of mucosal junction is seen above the contracted segment of the hiatal rosette, a hiatus hernia is present. The hiatal rosette is usually contracted, but when it is seen to be open most of the time, sphincteric incompetence is present. Reflux of gastric contents into the esophagus is a difficult diagnosis to make endoscopically. With the patient in the left lateral position, the pool of gastric secretions is on the greater curvature aspect and may not be of sufficient quantity to reach the esophagus and spill into it. As the endoscope is passed into the contracted segment in the diaphragmatic channel, it traverses the "submerged segment" (31) consisting of a tubular portion of the esophagus and a tubular portion of the stomach. Upon entering

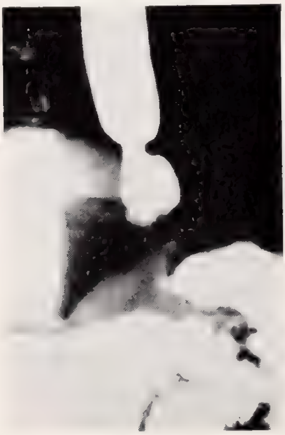

FIG. 11. Contractile ring at the superior end of the phrenic ampulla (A-ring). See *Figure 12* for endoscopic view.

the stomach, large folds are characteristically seen on the greater curvature aspect of the stomach, which to the examiner is located inferiorly. The anterior wall of the stomach is to the left and the posterior wall to the right. The lesser curvature is seen superiorly. Once the stomach is distended with air, and the instrument advanced through the cardioesophageal junction for about 10 cm, the re-entrant angulus appears on the lesser curvature aspect. This is a smooth semilunar curve which, to the endoscopist, separates gastric body from gastric antrum. In the distended stomach, no longitudinal folds are seen to cross over this angle which extends from the anterior to the posterior wall of the stomach. Many gastric ulcers occur on the angulus, and special attention should be paid to this area to exclude any pathological lesions. Contractile waves are usually not seen proximal to the re-entrant angulus, however, they are present distal to it. The antrum is recognized by its location distal to the angulus and by the peristaltic waves that circumferentially narrow it in a smooth regular fashion. There is no gross visual differentiation between the lining of the antrum and that of the proximal stomach. The pylorus always appears as a round, open dot at the apex of the antrum. Inflammation in the pyloric channel, or the duodenal bulb may cause eccentricity of the pyloric lumen with distortion of its round character. Once the instrument is passed into the duodenal bulb, as mentioned previously, no folds are present within the bulb and contractions are rarely seen. The descending duodenum is marked by its circular fold pattern which is present in the small bowel. Close inspection of the mucosa in the duodenal bulb reveals it to be velvety, due to the villi of the small bowel.

Relationship of Endoscopy to Upper Gastrointestinal Radiographic Series

A major indication for upper intestinal endoscopy is an x-ray that either shows a specific lesion (*Fig. 13*) or an x-ray finding that does not explain the patient's symptomatology. During endoscopy lesions seen on x-ray can be biopsied, cytology can be taken, and a direct visual impression can be obtained of its irregularity, its elevation and "stiffness" of the wall may be evaluated. Lesions in the fundus of the stomach are characteristically difficult to demonstrate by x-ray examination, and the patient with dysphagia and a negative x-ray may have a diagnosis confirmed by esophagogastroscopy. Patients with an ulcer in any portion of the stomach may have multiple biopsies performed to ascertain whether the ulcer is benign or malignant (Figs. 14 and

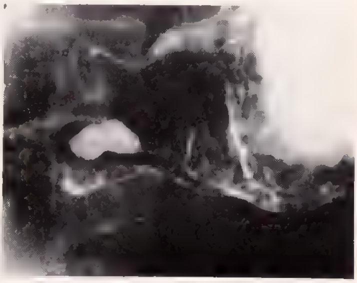

FIG. 14. Irregularly shaped ulcer with smooth edges in gastric antrum. See *Figure 15*.

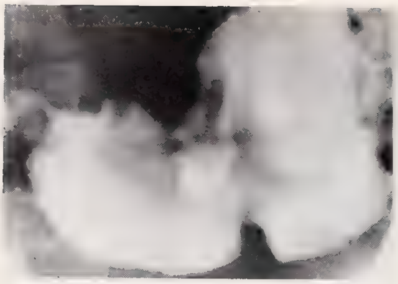

FIG. 16. Large ulcer in proximal antrum. This patient had anemia and weight loss, and the x-ray was interpreted as a malignancy. See *Figure 17*.

15). Biopsies of ulcers should be directed at the inner margin of the ulcer (Figs. 16 and *17*) and should not be taken from the base (only necrotic debris will be seen by the pathologist) nor from the rounded, edematous or bulging mucosal surface surrounding the ulcer (only "normal mucosa" may be present). If a submucosally spreading carcinoma has ulcerated, the mucosa up to the edge of the ulcer will be intact and the small endoscopic biopsy specimens of covering mucosa will not be deep enough to reveal malignant cells (*Fig. 18*). Biopsies may be directed through the gastroscopes with great accuracy and the exact site at the ulcer margin can be easily biopsied. When extensive mucosal involvement is present on x-ray, the course of treatment may depend on whether a carcinoma or lymphoma is found on biopsy (Fig. 19).

Japanese investigators have demonstrated that superficial gastric carcinoma may develop and be undetected by routine barium x-ray studies (33). In early gastric cancer, small patches of erythema, or edema of the mucosa may be visible to the endoscopist's eye and biospies may show small patches of carcinoma (*Fig. 20*). These patients may or may not have symptoms referable to the intestinal tract, and the Japanese have frequently discovered these by large scale screening endoscopic examinations. Patients with symptoms of "chronic dyspepsia" due to gastritis may have normal x-rays, but have the pathology discovered on upper gastrointestinal endoscopy (*Fig. 21*).

Complications of Upper Intestinal Endoscopy

The most common complication of upper gastrointestinal endoscopy is related to reactions to local anesthetic agents (28). As mentioned previously, I do not use local anesthetic agents, and I feel they offer no positive advantages. Patients properly sedated for endoscopy have no difficulty in accepting intubation nor do they voice reluctance if the procedure requires repetition at a later time.

Although I have encountered this problem once in over 6000 upper intestinal endoscopies, Morrissey (34) has mentioned that the most frequent serious complication of endoscopy in his institution is aspiration pneumonia, and he advocates gastric emptying prior to instrumentation. The one case I have seen occurred in a cirrhotic with actively bleeding varices who was heavily sedated for the emergency endoscopic procedure. This happened five years ago, and since then I have been reluctant to sedate gastrointestinal bleeders for emergency endoscopy.

Perforations are the most serious complication of endoscopy and the most common site is just above the cricopharynx in the posterior wall of the pharynx. During the attempt to enter the esophagus when the cricopharynx muscle is tightly closed (an uncooperative patient), the instrument may be pushed through the posterior pharyngeal mucosa and a hole will be created in the para-esophageal area. Very few perforations occur at the cardioesophageal junction, since it can now be visualized so easily with the endoscopic instruments. Gastric perforations may occur if the instrument is forcibly advanced into the stomach rapidly. The actual incidence of perforation is extremely low. No recent data is available on instrument perforations, but as of 1968, the perforation rate for esophagoscopy was 0.093 percent and for gastroscopy 0.074 percent (35). I believe that the current incidence is considerably lower than that and I have not seen a perforation-complication of upper intestinal endoscopy in 7 years. Partial perforation may result in the "benign air dissection" (36) phenomenon or may go unnoticed for several weeks before an abscess is found (37). Open perforations, if discovered immediately, should be closed and drained surgically (38).

Less common complications have been reported such as impaction of instruments in the esophagus or stomach and swelling of submaxillary or parotid glands (39).

Continuous electrocardiographic monitoring of patients during endoscopy has revealed only minor changes (40).

Enthusiasm for accurate diagnosis, coupled with the relative ease of passage of the newer endoscopes has given impetus to many nontrained (or poorly trained) physicians to "do endoscopy." Those of us who are committed to endoscopy cannot condone this although we are acutely aware that there is a lack of postgraduate training centers in the United States. The American Society for Gastrointestinal Endoscopy has proposed a set of guidelines for endoscopists (41), and it states that a minimum of 100 upper intestinal endoscopies be performed under supervision to qualify the physician as an endoscopist. I agree with those ASGE guidelines and believe that physicians must learn the endoscopic anatomy of the normal gastrointestinal tract and be familiar with normal as well as pathologic processes before attempting to pass the endoscope alone.

Cost of Upper Gastrointestinal Endoscopy

The standard upper intestinal panendoscopes cost approximately $4000.00. The available light sources (which can be used for all fiberoptic systems) range in price from $700.00 to $5000.00. Biopsy forceps cost approximately $75.00 each. There are several types of still and movie cameras which can be attached to the flexible endoscopes and television monitors are currently available permitting several people to watch endoscopy simultaneously. A fiberoptic teaching sidearm for one observer is available for approximately $1500.00. The incidence of repair of gastroscopes is considerably higher than colonoscopes because of the tendency for patients to bite down on the instrument and injure the external sheath, or even rupture several of the glass fibers. Even minor repairs cost several hundred dollors and a major repair of bundles and sheath may cost $1300.00. Fluoroscopy is not necessary for upper intestinal endoscopy and the instruments are usually quite portable and can be brought to a patient's bedside without difficulty.

Duration of Examination

A complete upper gastrointestinal panendoscopy should be completed within 15 minutes. With greater experience, the time can be diminished while in the examination of the acutely bleeding patient, the examination should not take more than a few minutes.

A thorough examination should not be sacrificed for the convenience of a rapid examination, but I have found that the reason a neophyte endoscopist takes longer to examine the stomach is not in the identification of disease, but in the study of normal structures which are quickly accepted as normal by the experienced fibroscopist.

Endoscopy in the Patient with Acute Upper Gastrointestinal Hemorrhage

Emergency endoscopy may be performed at the patient's bedside, in the intensive care unit, in the emergency room or in the endoscopic suite. Patients should have a preendoscopic gastric lavage with iced water or iced saline. My impression is that iced water lavage tends to temporarily stop bleeding, so that an endoscopic diagnosis can be more easily made. The bleeding patient should be endoscoped as soon as possible following the initial episode of bleeding. In over 95 percent of patients, a definite bleeding site can be established with absolute certainty. Following evacuation of stomach contents, the patient is reassured that after an initial episode of gagging, the gag response will subside and that the endoscopy will only take a few minutes. No medication is given routinely, and the endoscope is passed through the pharynx as noted previously. The actively bleeding patient is fearful of dying, and is usually eager to participate in any procedure which promises deliverance from his illness. I always explain to the patient that the examination is necessary, that it will not take over 5 minutes and that although sedation is usually given for the procedure, it may increase the patient's risk during the endoscopy. As soon as the cricopharynx is passed, the esophagus is insufflated with air and varices are sought. If upon entering the esophagus, a large amount of active bleeding is seen, an attempt should be made to clear the area with suction and air should be insufflated so that one may at least partially visualize the lumen and pass the instrument through the blood-filled esophagus into the stomach. Frequently, in the presence of actively bleeding varices, one may not be able to locate a bleeding site other than to say that the maximum bleeding is located within the distal esophagus. Once the site of bleeding is passed and the stomach is entered, no evidence of active bleeding will be seen and an adequate inspection of the stomach and duodenum may be performed. If no bleeding is seen the instrument is quickly passed through the esophagus noting whether esophagitis, erosions or ulcerations are present. The prior presence of a nasogastric tube frequently produces linear submucosal type erosions in the area of the cardioesophageal junction, and these must be differentiated from a Mallory-Weiss laceration. No fresh bleeding is produced by the nasogastric tube artifacts. Upon entering the stomach, a large pool of fluid and blood is frequently encountered along the greater curvature aspect of the stomach. If the pool is large, the tip of the scope may be immersed in the fluid, and visualization will be impossible. It is not feasible to attempt to suction the pool through the endoscope because clots will be impacted onto the end of the instrument and obscure vision. The tip of the scope should be flexed upward, taking it out of the fluid, and air insufflated into the fundal portion of the stomach. If the angulus can be seen above the level of fluid, the instrument should be passed down toward the angulus and beyond it into the antrum which contains no pool of blood because of its anatomical location when the patient is in the left lateral recumbent position. With the tip of the instrument in the fundus, if the pool of fluid and blood obscures the view of the angulus, one can usually hyperdistend the fundus with air and as the air raises up the angulus to fill the antrum, the instrument can be passed along the lesser curvature and under the angulus with direct vision. The antrum is then scanned while a bleeding site is sought. If active bleeding is seen issuing in a retrograde fashion through the pylorus, this is good evidence of an actively bleeding duodenal ulcer. Occasionally, one may see bubbly, frothy fluid issuing through the pylorus into the stomach. When the bubbles are blood-tinged this also is evidence of a bleeding duodenal ulcer. The instrument should then be passed through the pylorus, into the duodenal bulb. Frequently, an actively bleeding duodenal ulcer can be seen (*Fig. 22*), but occasionally a large amount of bleeding is seen issuing from the duodenal bulb but no specific site can be determined. The presence of active bleeding within the duodenal bulb is sufficient to make the diagnosis of a peptic ulceration within the bulb. If no bleeding site is found within the duodenal bulb, further attention must be paid to the mucosa of the stomach following withdrawal of the instrument through the pylorus. Diffuse gastritis must be ruled out, and special attention must be paid once again to the angulus where gastric ulcers are frequently located. The patient may be rotated from one side to the other in an attempt to shift the pool of fluid from obscuring the underlying mucosa. Upon withdrawal of the instrument through the esophagus, varices are once again sought. If bleeding in the esophagus can be ruled out, and the endoscopist can tell the surgeon that there is no evidence of specific gastric ulcer or diffuse gastritis, and that there is no duodenal ulcer or deformity of the duodenal bulb, one can safely assume that the bleeding site is hidden underneath the pool of debris in the fundus body of the stomach.

We have been able to draw this inference on several occasions, and be correct most of the time. The most important information that the endoscopist can provide is: 1. Whether varices are present and if they are bleeding; 2. Whether a duodenal ulcer is present, causing bleeding; 3. Whether there is diffuse gastritis; and 4. Whether there is any specific gastric lesion.

Even under the most difficult of circumstances, the information that the esophagus contains no varices and the stomach has no diffuse gastritis may be of great benefit to the surgeon and render the entire endoscopic examination worthwhile for the patient.

Operative Endoscopy

As the panendoscopes are passed through the distal esophagus, they may be guided past a Schatzki ring at the esophagogastric junction. If the Schatzki ring is smaller than the diameter of the instrument (1.2 cm), which is the same as the critical diameter for symptoms of dysphagia, the instrument may be passed forcibly through this ring, and rupture it. I have ruptured 25 Schatzki rings with the flexible fiberoptic instrument using this technique. Care must be taken to ensure that a rim of the entire circumference of the ring be visible around the entire periphery of the instrument, so that the instrument will not tend to slide to one side and cause perforation while pressure is applied. The tip of the instrument is placed in the "lock" position to stiffen the distal 6 cm of the tip. Gentle pressure is exerted and the instrument will be seen and felt to "pop" through the ring as it is ruptured (*Fig. 23*). A small amount of bleeding occurs following this maneuver, and has never been a significant problem. The instrument can then traverse the ring easily without any resistance. A tear can always be identified at the periphery of the ring, from which a slight amount of blood issues. Most patients achieve a lasting symptomatic relief from this rupture, but two patients in my experience have developed recurrent symptoms of dysphagia in 3 to 6 months. Each has had repeated flexible endoscopic rupture of these rings without permanent relief of symptoms. Care should be taken not to equate the forceful rupture of a Schatzki ring with the forceful passage of a fiberoptic instrument through a peptic stricture of the distal esophagus. In a peptic stricture, the narrowing is conical and narrows toward the stomach (Figs. 24, *25, 26*). A gentle attempt may be made to pass the endoscope through a peptic stricture, and if the stricture dilates and the instrument passes through, no problem arises. However, if the instrument is seen not to progess down the esophagus as pressure is exerted, the endoscope should be withdrawn and the site where the instrument was impacted against the wall observed. If there is bleeding at that site or avulsion of the mucosa is noted, no further pressure should be applied, and other means must be made to further dilate that stricture. The Schatzki ring can be ruptured because it is a thin membrane, and can be fractured with the blunt end of the instrument but this is not possible in the conical tapered stricture of peptic esophagitis.

Foreign bodies may be removed from the stomach using a wire snare, and

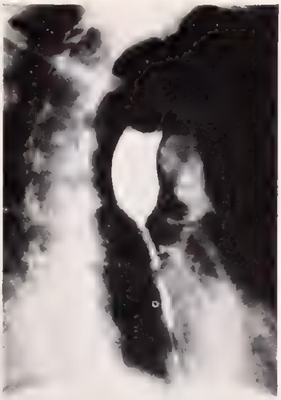

FIG. 24. Smooth conical tapering of stricture due to peptic esophagitis. See Figure 25.

such articles as thermometers, dental drills swallowed inadvertently during dental procedures, fruit pits and even gallstones have been removed with this technique.

Polypectomies may be performed in the stomach and duodenum (42, 43) and I have resected eight gastric polyps and two duodenal polyps (44) with the wire snare and cautery technique, as is used in removal of colonic polyps (Figs. 27, 28, 29, 30). Peristalsis tends to quickly evacuate polyps severed from the stomach or duodenum, and recovery of these resected polyps may be difficult unless adequate anticholinergic medication is given to prevent peristalsis. I have found that 15 mg of Probanthine® given intravenously causes complete cessation of gastric and duodenal activity rendering recovery of polyps easier. In one instance, a duodenal polyp was carried downstream by peristalsis, but castor oil produced the subsequent recovery of a lipomatous polyp.

Stopping bleeding is a major therapeutic use for the upper intestinal endoscopes and one can inject, through a catheter, a stream of vaso-constrictive material to the bleeding site, in an attempt to achieve hemostasis. We have used Levophed® and epinephrine solutions, with variable results. One may at-

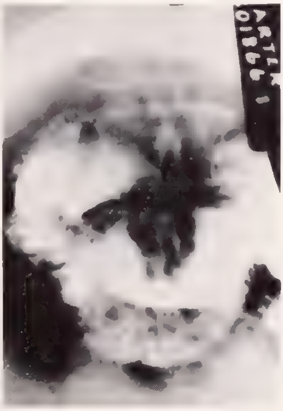

FIG. 28. Large filling defect in gastric antrum, shown on fluoroscopy to prolapse into the duodenal bulb. See Figure 29.

tempt to cauterize bleeding sites, either in stress erosions or in active peptic ulcers, and some success has been reported with this technique. There has also been a complication of perforation during the electrocoagulation attempt, and extreme care must be utilized to prevent this occurrence. One Japanese endoscopist has advocated the use of a clip onto a bleeding vessel through the endoscope, and this may be a feasible procedure for the future.

Gallstones impacted at the ampulla of Vater, and partially bulging into the lumen, may be removed by cautery-electrodissection of the lips of the ampulla around the gallstone, allowing it to fall into the duodenal lumen.

Cannulas may be placed into the pancreatic and biliary ducts with collections of fluid for cytological studies as well as for basic research purposes.

Precise placement of manometric pressure-recording tubes may be accomplished under direct vision in any portion of the esophagus or stomach. Dye material may be injected into the gastric mucosa through long needles for permanent marking of intestinal topography and for repeated study of the extent of growth/healing of lesions such as ulcers.

Concluding Remarks

The introduction of fiberoptic systems has caused a major revolution in upper gastrointestinal endoscopy during the past decade. The ease of passage of the flexible instruments and the clarity of visualization through them, combined with the ability to take multiple directed biopsies from any area of the gastrointestinal tract, have brought endoscopy from relative obscurity in medicine to a position as a well-accepted diagnostic procedure. Throughout the world, examinations are readily performed on ambulatory patients with a remarkably low incidence of untoward reactions. The value of intubation in acutely bleeding patients is well known, and I have reported on the safety of passing the endoscope through the esophagus filled with variceal veins (45).

The field of therapeutic upper intestinal fiberendoscopy is currently developing. Foreign bodies can be removed from the esophagus or stomach, esophageal rings can be ruptured, guide wires for dilatation of esophageal strictures can be placed under direct vision, gastric bezoars are being removed and one report has demonstrated drainage of a pancreatic pseudocyst by needle aspiration through the stomach (46). Gastric polyps are being resected with safety, and a number of techniques are available for the cessation of gastrointestinal bleeding. The future may present means of healing peptic ulcers by direct injection of therapeutic material, and chemotherapy may eventually be applied directly to gastrointestinal tumors.

The use of flexible endoscopy has brought us one step closer to the understanding and control of gastrointestinal disease processes.

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Application of the Flexible Bronchoscope

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Rigid bronchoscopy has long been a valuable procedure for the investigation of patients with malignant and benign endobronchial tumors, foreign bodies and inflammatory disease causing lobar or segmental atelectasis. The procedure has been marked by patient discomfort which often necessitates general anesthesia and by restriction of a rigid tube which limits visualization to major bronchi. Even with modifications such as the right angle bronchoscope, visualization and biopsy of peripheral bronchial and pulmonary lesions have rarely been possible.

In 1968, Ikeda reported his initial experience utilizing a fiberoptic instrument to examine the bronchial tree (1). During the ensuing years, he developed the prototype of the modern fiberoptic bronchoscopes currently in use. The most commonly used instrument in the United States is the Olympus Flexible Broncho fiberscope Type BF-5B2 (Fig. 1). This instrument has an outer diameter of 5.7 mm with an inner 2-mm channel through which secretions may be aspirated and a flexible brush or biopsy forceps introduced. Utilizing a remote control lever, the tip of the fiberscope may be moved through an arc of 160° (130° anterior and 30° posterior flexion). A teaching or lecture head is available which allows an instructor and student to share the view of the tracheal-bronchial tree. With the brilliant illuminating systems available, excellent 35-mm endoscopic photography or 8-mm cinematography is possible.

Materials

For local anesthesia, the following are recommended:
- 20 cc 2% lidocaine solution
- Topical anesthetic ointment
- Hand nebulizer
- Emesis basin
- Gauze pads
- Disposable 10-cc syringe

For collection of specimens, the following are required:
- Suction apparatus
- Suction trap collecting bottles
- Polyethylene connecting tubes
- Glass slides, cytologic fixative
- 1-cm squares of filter paper
- 10% formalin specimen jar
- Sterile gloves
- 10-cc nonbacteriostatic saline

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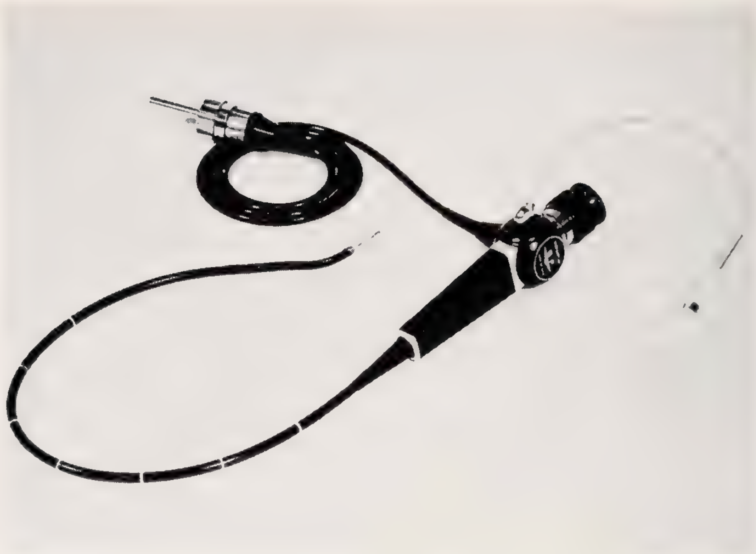


FIG. 1. Olympus Bronchofiberscope, Model BF-5B2 with flexible biopsy forceps in place.

Disposable 10-cc syringe

Ancillary supplies required are:

10-cc 1:100,000 epinephrine
Disposable 10-cc syringe

Cold sterilization of the fiberscope is accomplished by thorough washing with soap and water including the passage of a cleansing brush through the aspiration channel, followed by immersion in 2% PVP-I solution (Betadine®). This can be readily effected by immersing the instrument for 30 minutes in a ¾-inch diameter polyethylene tube with a corked distal end. This allows the control head of the fiberscope to remain out of the sterilizing solution. The solution is sucked into the aspiration channel with a disposable 10-cc syringe. After sterilization, the solution is washed out with saline and the instrument is dried with 10% isopropyl alcohol.

Optional equipment includes:

Through-the-lens 35-mm reflex camera (Olympus model FIT)
10-cc radiopaque iodized bronchography solution
60-cm length of polyethylene tubing with a wire obturator
Fluoroscope with table.

Collection of Specimens

Secretions are obtained via suction applied to a trap-collecting bottle connected to the 2-mm aspiration channel of the bronchoscope. An in-line "Y" connecting tube allows intermittent suction. The secretions are suitable for bacteriologic and cytologic analyses.

Brushings are obtained with a bronchial brush attached to a flexible cable and introduced through the aspiration channel of the fiberscope. For cytology, the brush is applied directly to glass slides which are immediately sprayed with a standard cytologic fixative. Alternatively, the brush may be immersed in a test tube containing sterile saline. With either method, the specimen must be delivered promptly to the cytology laboratory for processing. Several unfixed specimen slides are submitted to the bacteriology laboratory for gram and acid fast stains and, when indicated, special stains for fungi and pneumocystis carinii.

Utilizing the 2 mm biopsy forceps introduced through the aspiration channel, multiple biopsies may be obtained by direct vision or via fluoroscopic control. The specimens obtained are placed on 1-cm square pieces of filter paper which are immediately immersed in 10% formaldehyde. Where indicated, "touch prints" are made prior to immersion, or tissue may be placed in sterile saline for bacteriologic studies.

Methods

Careful explanation of the procedure is imperative to allay patient anxiety and obtain maximum cooperation. As premedication, we prefer codeine 60 mg, sodium phenobarbital 100 mg and atropine 0.4 mg injected subcutaneously 30 minutes prior to bronchoscopy. The patient may be seated in an otolaryngology examining chair or may be recumbent on a variety of examining tables. Since fluoroscopy is a frequent adjuvant to bronchofiberoscopy and bronchography is often a valuable addition to the procedure, the majority of our studies are performed with the patient recumbent on an x-ray table.

The nasal and oral pharynges are sprayed with approximately 5 cc of 2% lidocaine. Silicone® is applied to the distal lens of the bronchoscope to prevent fogging and lidocaine jelly or ointment is applied to the sides of the distal three inches of the bronchoscope. The instrument is then introduced through the most widely patent nasal orifice with or without the prior insertion of a latex nasal pharyngeal airway. The vocal cords are observed for motion and 1 cc of 2% lidocaine solution is introduced through the bronchoscopic channel directly onto the vocal cords. After approximately 30 seconds, the instrument is passed through the vocal cords into the upper trachea. This often causes a brief period of stridor which is always promptly overcome with the introduction of 1 cc of 2% Lidocaine solution. The bronchoscope is then passed into the desired lung and to the areas of the bronchial tree under study. Additional 1-cc doses of lidocaine are introduced as required to control coughing. This is usually necessary when entering a new division of the bronchial tree, particularly in the less dependent upper lobes and anterior segments. Aspiration of secretions, brushing of lesions and biopsies are then carried out as previously described. When indicated, a polyethylene tube is passed through the bronchoscopic channel into a specific segment under study and 10 cc of iodinized contrast media is introduced for bronchography.

Indications

Rath et al state that "the basic indications for fiberoptic bronchoscopy are the same as for rigid tube bronchoscopy" (2). In the main, this claim is true. However, qualifications, primarily due to the relatively small size (2 mm) of the aspiration channel, should be noted. In our experience, active profuse bleeding rapidly exceeds the aspiration ability of the small channel; and thick tenacious secretions, particularly when impacted into a lobar bronchus, often defy suction. In the latter instance, even when supplemented by saline lavage and enzymatic agents, aspiration may be unsatisfactory. A significantly larger biopsy of a major bronchus tumor can be obtained through the conventional rigid bronchoscope than that accomplished with the 2 mm biopsy forceps available with the bronchofiberscope. Finally, foreign bodies are so much more easily removed with the rigid bronchoscope, that most bronchoscopists agree that the removal of foreign bodies should not be attempted with the flexible instrument (3).

The bronchofiberscope offers many advantages over the conventional rigid bronchoscope. The procedure can be performed uniformly under local anesthesia with little discomfort or risk to the patient. Children as young as ten years of age and the elderly have been successfully examined without general anesthesia. Desperately ill patients may be examined, if necessary, at the bedside (4). Utilizing a simple adapter, flexible bronchoscopies are routinely performed on patients maintained by mechanical respirators (5). This is a particularly valuable diagnostic and therapeutic measure in patients requiring aspiration of obstructing bronchial secretions (6).

By far, the major advantage of the flexible fiberoptic bronchoscope is the ease with which it can be introduced into segmental bronchi, allowing visualization, aspiration, brushing and biopsy of previously inaccessible regions (7). It has been demonstrated that an additional one-third of the total bronchial tree has been brought into the view of the bronchoscopist with the new instrument and that the very periphery of the lung is accessible to the flexible brush and forceps (8).

I. Segmental and Subsegmental Disease

A. Neoplasm: The advantages of visualization, biopsy and bronchography are obvious. Numerous reports have attested to the high frequency of positive diagnoses in peripheral carcinomas. Ikeda noted that while the rigid bronchoscope visualized 159 of 360 primary bronchial carcinomas, an additional 140 carcinomas were seen with the bronchofiberscope (9). Thus the diagnosis by forceps biopsy was increased almost two-fold from 44.2% with the rigid scope to 83.1% with the flexible instrument. Most of those neoplasms visualized only with the flexible bronchoscope were in the heretofore inaccessible upper lobes.

Fennessey reported his experience using a transcatheter flexible brush to obtain bronchial specimens for cytologic analysis under fluoroscopic control (10, 11). A positive diagnosis of pulmonary malignancy was made in 88 of 127 (69%) primary bronchial carcinomas, 7 of 21 (33%) metastatic carcinomas and 4 of 10 (40%) lymphomas. Utilizing the fiberoptic bronchoscope to guide and position the bronchial brush and fluoroscopic control for lesions beyond the visual range of the bronchoscope, Richardson obtained a positive brush biopsy in 71 of 77 patients (92%) with endoscopically visible tumors and 39 of 50 patients

(78%) with nonendoscopically visualized carcinomas (12). In all, there were 200 patients in his study who had clinical and or radiographic abnormalities suspicious of pulmonary carcinoma. Of these, 130 proved to be carcinoma and 110 (85%) had a positive cytology. Interestingly, the diagnosis of carcinoma was established by bronchial brushing in three patients with hemoptysis and normal chest radiographs. One patient had a false positive cytology.

Solomon has shown that cytologic material obtained by fiberoptic bronchoscopy and brushing is superior to specimens obtained either by bronchial washing or from sputum (13). The technique of brushing has been expanded by Sanderson with the introduction of a controllable-tip brush (14).

Several groups are now engaged in studies of bronchial brushings of patients in high-risk carcinoma groups such as smokers over the age of 45 with positive sputum cytology and no localizing clinical or radiographic signs of carcinoma. At least 15 "roentgenographically occult tumors" have been uncovered in these subjects (15, 16). The routine use of flexible bronchoscopy and bronchial brushing in these groups, as a means of early detection of carcinoma, must await further observations.

The diagnosis of benign neoplasms and granulomas which are within the visual range of the flexible bronchoscope can usually be obtained by forceps biopsy. Solitary benign peripheral nodules are often encapsulated and do not communicate with a bronchus. In these instances, bronchial brushing rarely yields useful diagnostic information. It should be emphasized that a negative brush biopsy of a peripheral nodule does not preclude the presence of a malignant lesion. Such negative data is of no diagnostic value.

B. Inflammatory Disease: Pneumonias may be segmental in distribution, particularly when the segmental bronchial lumen is compromised by chronic inflammatory tissue, inspissated secretions, foreign body or neoplasm. Despite its previously noted limitations in aspirating thick secretions through the narrow 2-mm channel and in the removal of foreign bodies, flexible bronchoscopy offers easy examination of the diseased segmental bronchus and sufficient suction capacity to obtain valuable culture material. This procedure is of especial importance in patients with pneumonias which are slowly resolving or unresponsive to antibiotic therapy.

II. Peripheral Bronchopulmonary Disease

Utilizing the flexible fiberscope, the bronchoscopist is called upon to investigate two types of peripheral pulmonary lesions, (A) solitary nodules and (B) diffuse pulmonary diseases confined to a segment, lobe or more than one lobe.

A. Solitary Nodules: Zavala (17) and Marici (18) have reported high diagnostic yields in single or several widely dispersed pulmonary nodules, benign or malignant. Since these lesions are beyond direct vision, fluoroscopy with image intensification must be employed. Despite this invaluable visual aid, the operator frequently finds that he can maneuver his brush into the correct segment or subsegment, but the fifth and sixth order bronchioles which lead to the lesion in question defy instrumentation. In our experience, bronchoscopic brushing of peripheral nodules is of limited value as an aid to therapy no matter what the yield. Almost all nodules increasing in size will require resection. Benign tumors and granulomas which have not changed over a period of time need not be removed. In neither instance will the cytologic information be crucial. It is the poor surgical risk patient with a radiographically undiagnosable nodule, and no previous roentgenograph for comparison, who may benefit from a definitive preoperative bronchoscopic diagnosis. In our experience, such instances are rare.

B. Diffuse Pulmonary Disease: One of the most valuable applications of fiberoptic bronchoscopy is the relative ease and safety with which a forceps biopsy of peripheral lung tissue may be obtained. Lung biopsy with a flexible forceps passed through a rigid bronchoscope was described by Anderson in 1965 (19). Several subsequent reports have established the value and low patient risk of this procedure (20, 21). Our results with forceps biopsy in 52 patients with diffuse disease involving one or more lobes of the lung are shown in Table I. Pulmonary tissue was obtained in 37 of the 52 patients (65%). Of these, 29 were diagnostic. Thus, the diagnosis was established in 56% of the 52 patients with diffuse lung disease. Table II shows the diagnostic yields of these lung biopsies. The diagnosis of such opportunistic infections as pneumocystis carinii is particularly gratifying since the patients so afflicted tend to be gravely ill and early diagnosis is mandatory for effective treatment (22, 23).

TABLE I

Forceps Biopsy in 52 Patients with Diffuse Pulmonary Disease

Total Lung Specimens Obtained	37
[a] Diagnostic Biopsy	29
[b] Nondiagnostic Biopsy	8
Inadequate Specimens	15

TABLE II

Diagnoses By Forceps Biopsy in 29 Patients with Diffuse Pulmonary Disease

	Number of Patients
Sarcoidosis	11
Metastatic carcinoma	7
U.I.P.	4
Slowly resolving pneumonia	3
Pulmonary asbestosis	2
Pneumocystis carinii pneumonia	1
Eosinophilic pneumonia	1

The following three patients demonstrate the value of flexible forceps lung biopsy in the diagnosis of diffuse pulmonary diseases:

1] A 42-year-old black woman was admitted to The Mount Sinai Hospital July 26, 1973. She had anorexia, a 20-pound weight loss, dyspnea and a nonproductive cough. Her chest roentgenograph (Fig. 2A) revealed bilateral two-to-three centimeter, nodular pulmonary densities. Biopsy (Fig. 2B) showed lung tissue with noncaseating epithelioid granulomas consistent with sarcoidosis. A subsequent Kveim test was positive. With adrenocorticosteroid therapy, her chest roentgenograph cleared.

2] A 70-year-old white man was admitted to The Mount Sinai Hospital on March 26, 1974 with malaise, anorexia and a 15-pound weight loss. Liver biopsy and gastrointestinal roentgenographs were normal. His chest roentgenograph (Fig. 3A) revealed multiple pulmonary nodules of varying sizes. Forceps biopsy (Fig. 3B) showed lung tissue invaded by adenocarcinoma. At autopsy four months later, a carcinoma of the tail of the pancreas was found.

3] A 27-year-old white man was admitted to The Mount Sinai Hospital on December 3, 1973 complaining of increasing shortness of breath and cough of six weeks duration. His peripheral blood smear showed 23% eosinophils. His chest roentgenograph (Fig. 4A) demonstrated opacification of the lateral aspect of the left upper and mid-lung zones. Forceps biopsy (Fig. 4B) revealed pulmonary tissue with interstitial edema, collagen formation and infiltration by eosinophils consistent with an eosinophilic pneumonia. The roentgenograph returned to normal in four weeks with adrenocorticosteroid therapy.

The major complication has been pneumothorax, none exceeding 20% and none requiring intubation. While bleeding is usually minimal, two postbiopsy hemorrhages occurred of 100 cc and 200 cc respectively. No patient required a blood transfusion.

The results of fiberoptic lung biopsy should be compared with other "closed" biopsy techniques such as needle biopsy (24) or trephine drill biopsy (25). In both of these procedures, the reported complications far exceed those of transbronchial biopsy (26, 27). While drill biopsy has the most diagnostic yield (28, 29), complications, including death, exceed that of the transbronchial technique. We now attempt a transbronchial biopsy in all patients with undiagnosed diffuse pulmonary disease. Only after failure with flexible forceps biopsy via the fiberscope do we consider open lung biopsy.

III. Hemoptysis

The limited aspiration capacity of the current fiberoptic bronchoscopes precludes its use in massive pulmonary hemorrhage. However, less exuberant bleeding can be investigated more thoroughly with the flexible instrument than with rigid tube bronchoscopy. Segmental and subsegmental bleeding sites can be visualized and specimens obtained far beyond the range of the rigid bronchoscope. Smiddy has reported success in localizing bleeding sites employing segmental lavage with the bronchofiberscope in two patients after failure to identify the source of bleeding with the rigid bronchoscope (30).

IV. Bronchoscopy in Patients with Assisted Ventilation

With a simple adapter, the flexible bronchoscope can explore the bronchial tree while patients are maintained on assisted ventilation. Frequently, valuable bacteriologic specimens can be obtained. When secretions are not inspissated, obstructed airways can be lavaged and cleared. Shinnick described a wide range of applications of the flexible instrument in 28 bronchofiberscopic examinations performed during mechanical ventilation (5).

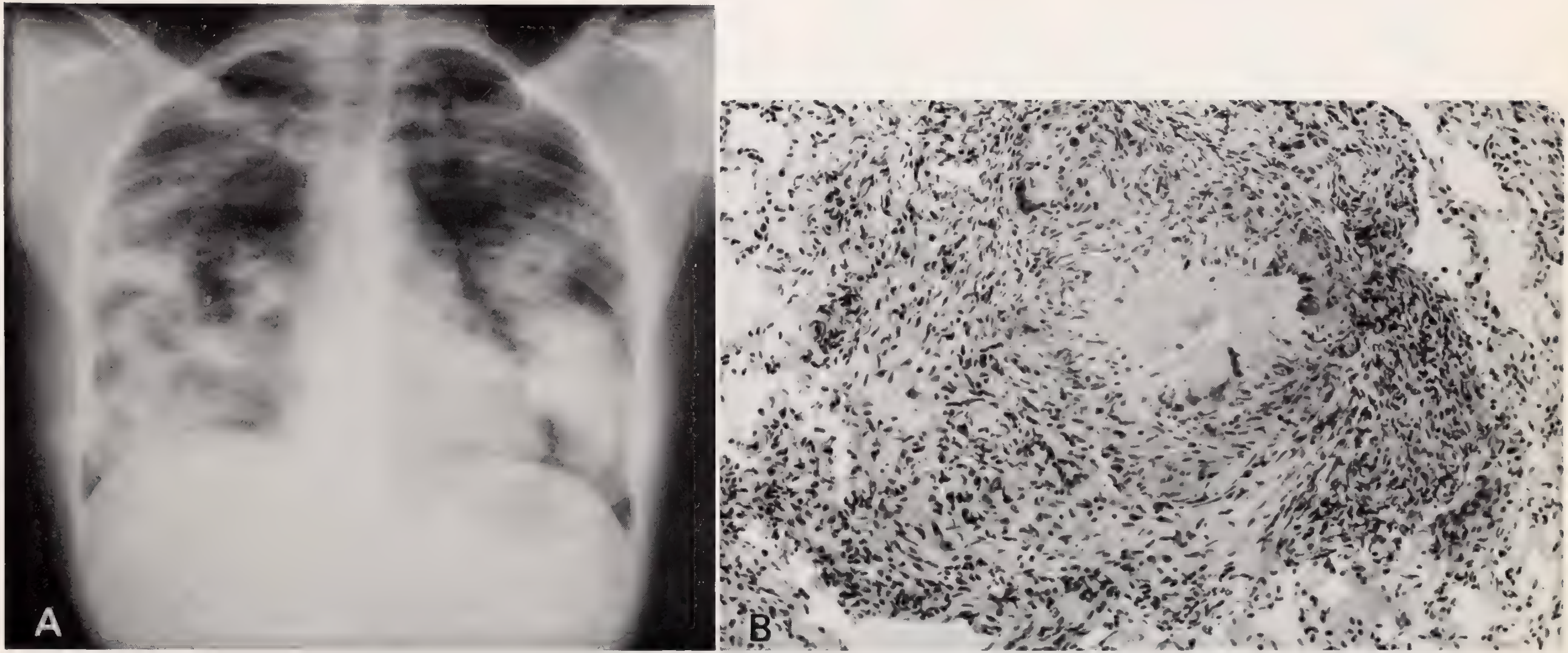
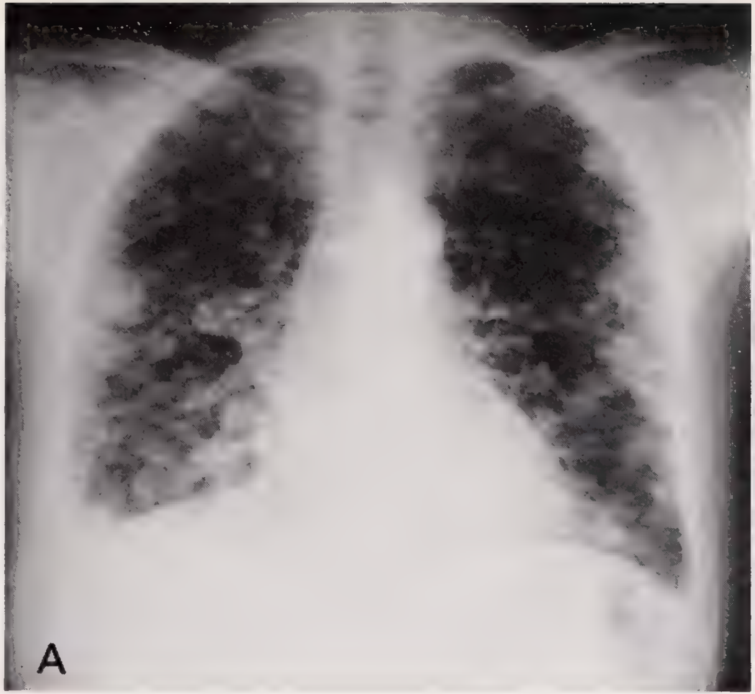


Fig. 2A. Chest roentgenograph of a 42 year-old black woman showing bilateral "cannon-ball" densities.

Fig. 2B. Lung biopsy specimen obtained with flexible forceps inserted through the bronchofiberscope which shows lung infiltrated with noncaseating epithelioid granulomas consistent with sarcoidosis.



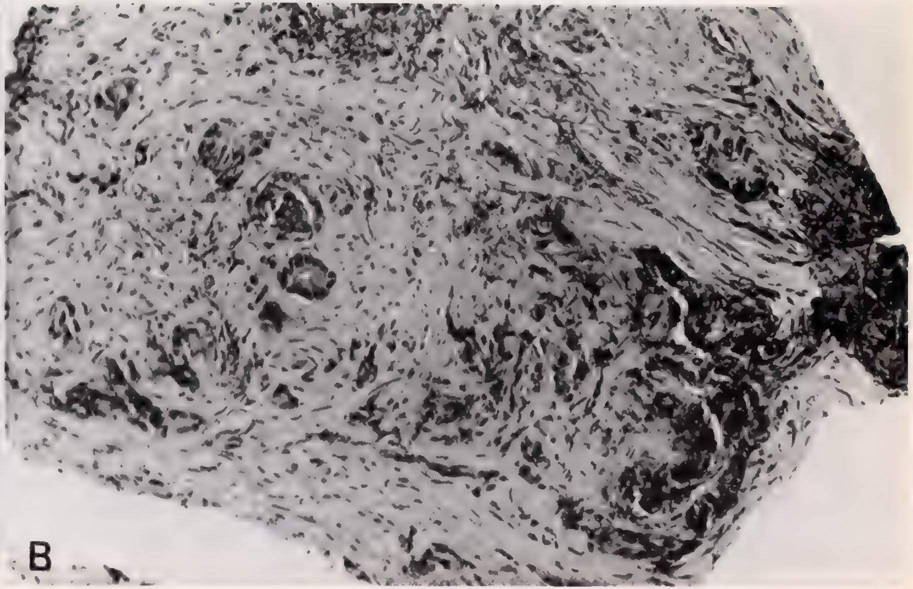


Fig. 3A. Chest roentgenograph of a 70-year-old white man demonstrating bilateral, sharply circumscribed pulmonary nodules of varying sizes.

Fig. 3B. Flexible forceps lung biopsy specimen revealing pulmonary tissue invaded by adenocarcinoma with glandular features.

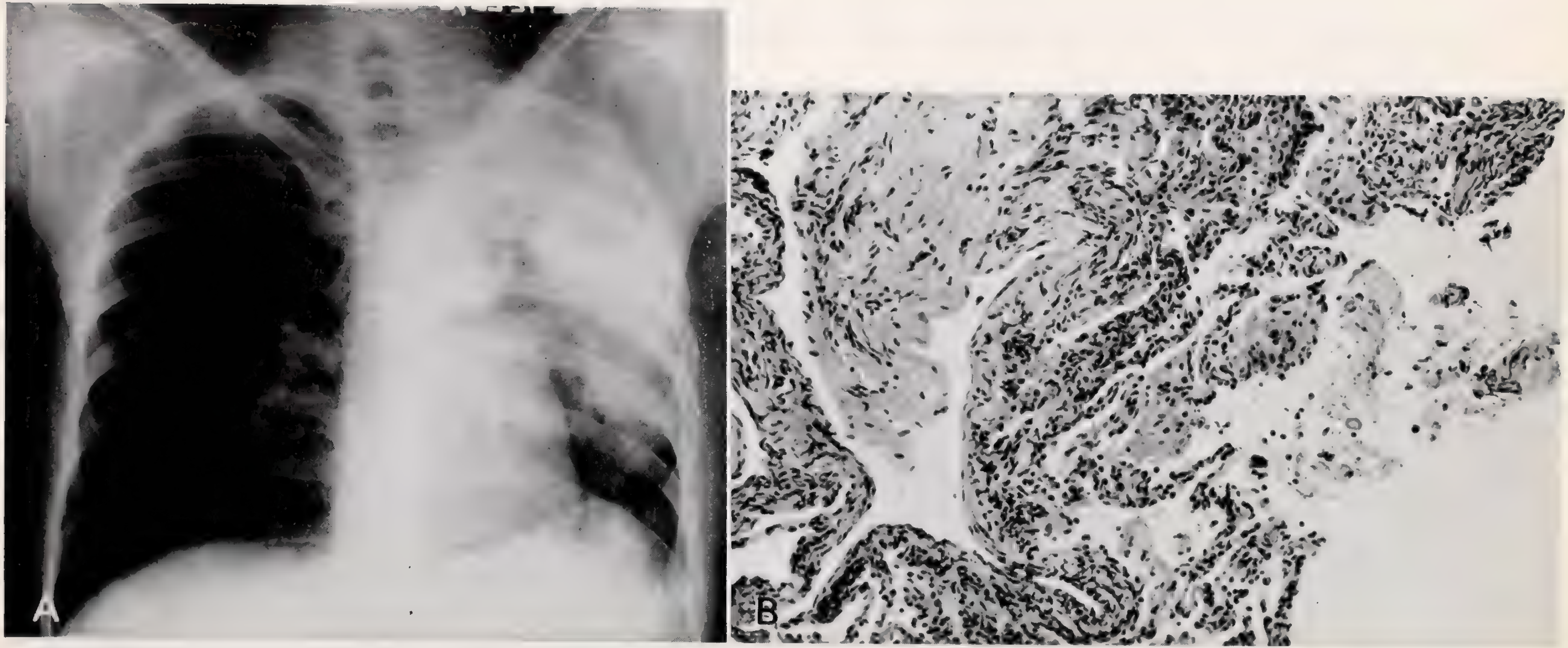


FIG. 4A. Chest roentgenograph of a 27-year-old white man with opacification of the entire periphery of the left upper lobe, sparing the lingula.

FIG. 4B. Flexible forceps lung biopsy specimen demonstrating interstitial edema and infiltration by polymorphonuclear leucocytes; with oil immersion these cells proved to be eosinophils consistent with eosinophilic pneumonia.

V. Research

The ease with which the fiberscope can be passed and tolerated offers an opportunity to study the physiology and biochemistry of the bronchial tree. Peripheral gas and mucous samples have been analyzed and the flow of the "mucous blanket" observed (31). This is a growing source of animal and human data which is now beginning to be tapped.

Complications

An extensive survey by Credle et al of 24,521 fiberoptic bronchoscopies has contributed greatly to the understanding of the spectrum of complications of bronchofiberoscopy (32).

The complications should be considered under four headings, those due to A) Premedication, B) Local Anesthesia, C) Bronchoscopic Procedure, and D) Ancillary procedures (brushing, biopsy and bronchography).

A. Premedication: Four serious episodes of respiratory depression due to excessive premedication with narcotics have been reported by Credle. All required resuscitation and survived. We have experienced no untoward reactions to our usual premedication "routine" of codeine, sodium phenobarbitol and atropine as outlined in the *Methods* section of this paper. However, this routine is varied according to the patient's overall medical condition. Codeine is withheld from patients with evidence of respiratory depression and atropine is not given to the aged or patients with a history of cardiac disease. An occasional patient, ill with severe obstructive pulmonary disease, receives no premedication. Finally, intubated patients, receiving assisted ventilation, do not require premedication.

B. Local Anesthesia: Eight major complications, including one death, have been reported due to local anesthesia. These include three respiratory arrests, three seizures, one methemoglobemia and one cardiovascular collapse with death. Seven of the eight complications were due to excessive Tetracaine®. One seizure occurred with the use of lidocaine. Complications due to Tetracaine are well-known. The margin between therapeutic effect and toxicity is small; absorption from the respiratory tract is high; toxicity may be sudden and catastrophic; and its action is relatively prolonged. Palmer reported 33 adverse reactions and nine deaths utilizing Tetracaine for esophageal and gastric endoscopy (33). While lidocaine is readily absorbed from the respiratory tract, its margin of safety is much greater than Tetracaine. Utilizing from 10 cc to 20 cc of 2% Lidocaine (including oral-nasal nebulization and 1-cc increments as the examination proceeds down the respiratory tract), we have encountered no adverse reactions.

C. Bronchoscopic Procedure: The only reported complications of the passage of the fiberoptic bronchoscope have been laryngeal spasm, bronchospasm and hypoxemia. A mild episode of laryngeal spasm, lasting about 30 seconds, often occurs when the fiberscope is passed through the vocal cords. This is easily overcome by the installation of 1 cc of 2% lidocaine and should be entirely prevented by adequately anesthetizing the vocal cords prior to passage. While two patients in Credle's survey suffered from severe bronchospasm requiring resuscitative measures, we have not encountered this complication.

Karetzky has noted a decrease in arterial PO_2, as much as 21 mm Hg with an average decrement of 12 mm Hg in 14 patients, with the fiberscope at the carina (34). For this reason, every patient with hypoxemia should receive oxygen during the procedure. This can be adequately accomplished by the administration of oxygen by nasal prongs if the fiberoptic bronchoscope is passed transorally, or via a single nasal cannula in the opposite naris, if the transnasal route is employed. When passing the bronchoscope through an endotracheal tube while the patient is receiving ventilatory assistance, the FiO_2 should be increased with electrocardiographic monitoring for arrythmias (35).

D. Ancillary Procedures: Pneumothorax, hemorrhage and, in one instance, a lost brush have been reported due to ancillary procedures. We have encountered no complication of brushing. In the 122 patients who underwent forceps biopsy, almost all multiple biopsies, we experienced two patients who "hemorrhaged," one approximately 100 cc and the other approximately 200 cc. The latter patient required brief endotracheal intubation for aspiration of the accumulated blood. None required transfusion. Attempt to biopsy peripheral lesions or to obtain lung biopsies must be accompanied by an increased incidence of pneumothorax and hemorrhage. In our series, six pneumothoraces were identified postbiopsy, none greater than 20% and none required intubation of the thorax. Obviously, biopsies should always be limited to one lung.

Who Should Perform Fiberoptic Bronchoscopies?

In a recent editorial, Tucker et al strongly urged that only individuals trained in rigid bronchoscopy should be qualified to perform fiberoptic bronchoscopy (36). A flurry of subsequent letters and editorials refuted this position. These latter writers cited the ease of fiberoptic instrumentation and the wealth of data with minimal complications obtained by workers with no previous training in rigid tube bronchoscopy (37, 38). We have found that a "medical" approach to bronchoscopy is of unsurpassed value. The medical bronchoscopist usually brings an interest and understanding to the patient's problem, gained by direct or indirect prior involvement in his care. The medical bronchoscopist is usually amenable to altering the "routine" when unexpected findings are encountered.

Certainly, an operator experienced in the internal normal and abnormal anatomy of the bronchial tree must supervise each procedure. We have established the following list of criteria for certification of the competence of our staff for bronchoscopy:

1] Trainees must attend regularly scheduled sessions for a period of at least one year.

2] Each trainee should perform at least 30 flexible bronchoscopies.

3] A senior member of the faculty, who shall have been certified as a qualified bronchoscopist, must be present at all bronchoscopies and supervise the trainees.

4] This faculty member will certify in a log the successful performance of each procedure by the trainee.

5] The director of each service or division shall certify in writing the competence of each trainee at the completion of the training period.

Summary

Fiberoptic bronchoscopy has rightly ascended in popularity since its introduction by Ikeda in 1968. The ease of introduction, acceptance by the unanesthetized patient, superior visibility of the bronchial tree and low incidence of complications have established this flexible instrument as the preferred bronchoscope when investigating peripheral lung nodules, diffuse interstitial pulmonary diseases and pulmonary infections. It is also strongly recommended for detecting the site of bleeding in most cases of hemoptysis and for use in intubated patients. Massive pulmonary hemorrhage, thick inspissated secretions and foreign bodies are contraindications. A qualified fiberoptic bronchoscopist need not receive prior training in rigid bronchoscopy.

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In Memoriam

RALPH M. COLP, M.D.

1893–1974

Ralph Colp was born in New York City on January 26, 1893. His father, a pharmacist, owned an establishment at the corner of Cornelia and Bleeker Streets in Greenwich Village. Like so many outstanding New Yorkers, Dr. Colp was educated in the public schools of the City. He attended Stuyvesant High School and, in 1911, graduated from Columbia College and was elected to Phi Beta Kappa. He completed his undergraduate medical studies at the College of Physicians and Surgeons in 1915 with honors, including election to Alpha Omega Alpha.

After graduation, he served as surgical intern at Presbyterian Hospital and as assistant resident at Sloan Maternity Hospital. After a two-year term of service in the U.S. Army Medical Corps during World War I he was, in 1919, appointed to the Visiting Staff at Beekman Street Hospital, then the Volunteer Hospital, and was made an Instructor in Surgery and Anatomy at the College of Physicians and Surgeons. This appointment was of great importance to his development, for Dr. Colp's remarkable sureness and skill in the operating room were based on his encyclopedic knowledge of human anatomy. Later, after study and research in the anatomical laboratory, he introduced the operation of bilateral excision of the submaxillary gland, for treatment of Ludwig's Angina, the often fatal, phlegmonous infection of the floor of the mouth. Many lives were saved by this procedure until the introduction of antibiotics made the treatment obsolete.

Beekman Street Hospital, later renamed the Beekman Downtown Hospital, to whose staff Dr. Colp was appointed in 1919, also played an important part in his development. In 1923 he became a full Attending and together with Dr. Robert Kennedy established an outstanding surgical service which soon became known worldwide for the management of injury and especially in the treatment of the patient with multiple trauma. Dr. Colp's papers on fractures of the head of the radius, periarterial sympathectomy for lower extremity fractures and others, reflect his interests during this period.

His long association with The Mount Sinai Hospital began in 1923. It was to last for fifty years, during which he was to become one of the world leaders in the surgery of the gastrointestinal tract. In 1932, after ten years of work and growth, he was promoted to the rank of Associate Surgeon. This was especially important, since, in those days, the Associate ran the service for the summer months. Less than two years later, he was to be a full Attending, at first in charge of the Colon Service, later, of the Gastric Service. Concomitant was his appointment as Clinical Professor of Surgery at Columbia University. Reluctantly, he left Beekman Street to devote his full attention to his Mount Sinai Service.

Here, on the Colp Service, the concept of the multidisciplinary team was introduced long before it became fashionable. Attached to the service was an internist, Dr. Samuel Averbuck; a psychiatrist; a gastroenterologist, Dr. Asher Winkelstein; and a gastrointestinal physiologist, Dr. Franklin Hollander.

Ward grand rounds were formal, crowded with staff and visitors. After presentation of the case by the House Surgeon, demonstration of the pertinent x-rays and the surgical specimen, the case was open for discussion, which included medical, psychiatric and physiologic aspects. Later, these were conducted off the ward as a formal conference.

Here at grand rounds young surgeons were taught the discipline needed to lead a productive and organized professional life. As one observer and colleague of Dr. Colp, Dr. Lester Blum put it:

> As if by magic, on the stroke of nine, Dr. Colp would rise and say, "The first case will be presented by . . .," and in an equally magical fashion, seemingly without consulting the clock which was now precisely on the hour of ten, he would say, "Gentlemen, thank you."

Dr. Colp was a strikingly handsome man. Quite tall, very erect, impeccably dressed and groomed, he stood out among those about him and at once became the central figure in a group. He had great dignity and bearing. His rather formal manners included handwritten thank-you notes in response to even the smallest gifts and favors. His good manners were most in evidence in his relations to the patients on his service. They were treated with the kindness and consideration thought only to be the prerogative of wealthy private patients. He had the rare ability to make each ward patient feel that his case was unique and important, as indeed it was, for Dr. Colp brought his knowledge and skill just as surely to bear on the problem of a minor hand infection as to a complex gastrointestinal problem.

He drove his house staff hard, but trained them well and supported them loyally, if they had integrity and ability.

It was in the operating theater that he shone most brilliantly. The incision was made on the stroke of the hour listed on the schedule. The operation was performed rapidly, with no wasted motion. His technical skill was extraordinary; he used either hand with equal facility. No one could, after opening the abdomen, assess more accurately and expeditiously the implications of what he saw and felt. The course of action being determined, the operation proceeded, using sharp dissection throughout. The display of pathology and the mobilization of structures was made possible by his remarkable deftness and a profound knowledge of anatomy both in normal and pathologic states. Visitors from all parts of the United States and the world came to observe him work. The author of this obituary remembers assisting Dr. Colp in an historical operation, the transthoracic division of the vagal trunks in two ulcer patients, while the great gastric surgeon, Dr. Polya of Budapest, observed.

Dr. Colp later understood that the failure of this procedure (later repeated successfully by others) was due to the imperfect knowledge at that time of pancreatic and gastric physiology. He set up a fellowship for the study of pancreatic function. The first Ralph Colp Fellow was Dr. Henry Doubilet, who made important early contributions. The second Ralph Colp Fellowship was given to Dr. David Dreiling in July 1946.

At the time of Dr. Dreiling's graduation from the House Staff, Dr. Colp called him in and said, "Dreiling, you can join me in my office and make a lot of money, or go into the lab and do research on biliary and pancreatic physiology. You'll get only $600 a year. Take your choice." Dr. Dreiling made his choice, and several books and 260 papers later, still praises the foresight of the man who, though a brilliant clinical surgeon, understood the inadequacy of the scalpel in solving complex physiologic problems.

Many other young men and associates were encouraged by Dr. Colp. All whom he influenced were better doctors and better surgeons for having worked with him. These men are to be found in practice in New York and scattered about the country where, in almost every instance, they have attained a high rank on the surgical service of their hospital and professional rank in their medical school.

During the years at Mount Sinai, he added fifty scientific papers to the twenty-four he had already written. These elegant contributions covered the surgery of the pancreas and biliary tract and gastric surgery in all their ramifications, with particular emphasis on the treatment of peptic ulcer.

In 1950, he was elected by his colleagues to a four-year term as President of the Medical Board. In 1952, at the time of the Hundredth Anniversary Celebration of the founding of The Mount Sinai Hospital, he was presented with "The Gold-Headed Cane." This was a replica of the one enshrined in the Royal College of Physicians in London. The original cane had been passed from one outstanding clinical teacher to another from the late 16th to the early 19th century. The occasion of the "Mount Sinai Cane" was to honor a most outstanding clinical teacher, which indeed he was.

He retired from active service on the wards of The Mount Sinai Hospital in 1955. However, he continued to practice, carrying a large surgical load of private patients until he stopped operating and closed his office in his 70th year. He was presented with the Jacobi Medal of the Alumni Association of the hospital for outstanding service. At the time of the inception of the medical school, he was given the rank of Professor of Surgery and Director of Surgery Emeritus. He was a consulting surgeon to the Mount Sinai, Beekman-Downstown, Beth Israel, French, Harlem, Columbus and Long Beach Hospitals. He was a Senior Fellow of the American Surgical Association, and a Diplomate of the American Board of Surgery (Founders Group). He was a Fellow of the American College of Surgeons and a past Governor, and a member of its Credentials and Judiciary Committees, a Senior Fellow of the American Gastroenterological Society, a Fellow of the New York Academy of Medicine and former Chairman of the section on surgery. He was a Senior Fellow of the New York Surgical Society and a past President of that notable organization. He held honorary fellowship in the Mexican College of Surgeons and was an honorary member of the Central Surgical Society.

Thirty years before his death, he began to think of his retirement. He became intensely interested in travel and archaeology and began to take long trips to the various parts of the world in which he had become interested. Characteristically, before he departed on a trip, he would read voluminously in order to steep himself in the background of the place to which he was going. Following his retirement from practice in 1963, he spent more time in his travels. A touching article entitled "Invitation to Old Age" was written by him and appeared in a symposium on aging, published in November, 1972 in the Bulletin of the New York Academy of Medicine. In this small article, he reveals the joy and stimulation he obtained from his journeys.

He died peacefully of arteriosclerotic heart disease, after a long hospitalization at The Mount Sinai Hospital. He is survived by his third wife, Cecile and by Ralph Colp, Jr., a son of his first marriage.

Few men are able to see themselves clearly. Even less is it possible for them to concentrate, in a few written words, the essence of the meaning of their lives. Dr. Colp, quite privately, wrote the following inscription on the fly-leaf of a small volume, "Lister As I Knew Him," by John Rudd Leeson, which he presented to Ralph Colp, Jr., who has graciously consented to its use:

> April 9, 1963
>
> This book is inscribed to my son, Ralph, by his father, on the day of retirement from surgical practice covering almost forty-eight years. Years enriched by the learning from experiences in a thrilling era of scientific advances, illuminated by the gratitude of hundreds helped, and further embellished by the recognition of his moral integrity, intellectual honesty and professional attainments, by his colleagues and friends.

BERNARD SIMON, M.D.
for the
EDITORIAL BOARD

Every Step of the Way

LAWRENCE J. ROOSE, M.D.

AND

HOWARD D. ZUCKER, M.D.

Abstract

Comprehensive medical care every step of the way must involve doctors in the total life experience of the patient, not only in his organic illness. Sometimes doctors need more help than does the patient in coping with the intense and conflicting feelings mobilized by the situation of the patient and the family, particularly when the patient is seen as a dying person. At such times good management is hampered, and responsibilities are often avoided—sometimes to the point of abandoning the patient. The goal of the liaison psychiatrist is to help doctors in patient management. In this case report unnecessary medication and emotional abandonment were avoided by the liaison psychiatrist's intervention in a situation where the patient was disturbed but exhibited no severe psychopathology. The patient responded well to simple warmth and to sustained, informed interest, while the medical staff reassumed normal interchange with the patient.

Introduction

In recent years increasing attention has been focused on the care of the patient with limited life expectancy, the dying patient. Among the factors generating this interest are the rapid increase in the use of liaison psychiatry in general hospitals, the increased knowledge about separation and grief throughout the life cycle (1, 2), and the societal reaction against the depersonalization of highly industrialized urban societies and their large impersonal hospitals. This last factor finds specific expression in the intense interest in medical ethics which has resulted in the formation of new institutions (3) and in the inclusion of topics concerning medical ethics in the curricula of many medical schools.

The care of the dying patient is the subject of an increasing body of literature (4, 5). The difficulties created by the anxieties of those who are close to the dying patient are commonly acknowledged. The modes of coping with these anxieties tend to be neglected in favor of studies of the psychodynamics of patient and family. Specific directions for the treatment of patient and family appear to be of greater importance than helping doctors to become aware of their own anxieties and how they influence their therapeutic efforts. The impact of this learning experience differs from group to group. Student nurses and medical students appear to be closer to their own feelings and more openly expressive of them than do interns, residents, and attending physicians.

This presentation is intended to help those who teach young doctors about the

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care of the dying patient and to illustrate how teaching encounters can be most successfully utilized.

The psychiatric liaison service at The Mount Sinai Hospital of New York has for over 30 years assigned psychiatrists to the general hospital wards. Their functions include service to patients and the teaching of nurses, medical students, housestaff members, and attending physicians. On the medical service, a liaison psychiatrist is attached to each medical unit. At times a psychiatric resident being trained in liaison consultation is also on the unit. Housestaff teaching is largely carried on in informal discussions but more formally through biweekly conferences. The patient to be discussed is chosen by mutual agreement between the chief resident and the liaison psychiatrist. Statistical analysis reveals that almost one-half of the conferences deal with the dying patient in one way or another. The goal of liaison teaching is to help the physician more effectively to meet the emotional needs of his patients rather than routinely to refer them to a psychiatrist—as Osler put it, "To walk every step of the way with the patient."

Let us observe one of the biweekly liaison conferences on the medical service of this large voluntary metropolitan hospital. Present at this conference were Dr. Zucker, the liaison psychiatrist who conducted the conference, Dr. Stan, the third-year psychiatrist resident on liaison duty, Dr. Alman, the liaison service psychologist, two social workers, a social work supervisor, the housestaff, (Dr. Weiss, chief resident, Dr. Sterling and Dr. Berg, assistant residents, Dr. Jay, Dr. O'Brien, Dr. Charles and Dr. Poland, interns), and Dr. Skinner, an intern on rotation through an elective month in psychiatry. All names except those of the authors are fictitious. Dr. Roose, director of the Psychiatric Liaison Service sat in, as usual, as recorder. This case report, taken in longhand is unedited except for purposes of clarity and the interposition in brackets of the concurrent thoughts of Dr. Zucker.

The patient to be discussed was selected for conference by the psychiatric resident, Dr. Stan, and the liaison psychiatrist, Dr. Zucker, because the former reported that the intern, Dr. Jay, caring for the patient, a young man with apparently terminal leukemia, was talking more and more about the patient to others on the housestaff, who were getting more and more "up-tight." Yet they did not want a psychiatrist to disturb the dying boy. The psychiatric resident also had doubts about disturbing him. In selecting this patient for discussion the liaison psychiatrist hoped to relieve the staff's anxiety and to receive permission to become involved in his treatment.

Case Presentation

The history given by Dr. Jay, the patient's intern, concerns a 22-year-old man with acute myelogenous leukemia, now of 1½ years duration. He has had two previous remissions, the first 16 months before the present admission, and the second, in the early part of the month of admission. The second remission lasted only two weeks. At this time, he was readmitted in critical condition with life expectancy extremely limited. He had been in the "life-island" during his first admission, where it was noted that he was rather paranoid. The life-island treatment had little effect and, indeed, there is controversy about the effectiveness of that procedure as a whole. He has had two courses of "red-death" treatment (daunomycin) but both times had "broken through." The remissions have tended to become shorter and shorter. In looking at the patient as a person, Dr. Jay feels that the patient is very scared. He believes that the patient knows that he has a fatal disease. The patient has become increasingly irritable, cursing the nurses, for example. Today he is a bit paranoid. He has been much frightened by the fact that he has a fever, although he knows that it is a drug-induced fever. Publicly the patient states that he has a primary refractory anemia. He does not talk about death although Dr. Jay felt that he was almost on the point of mentioning this several days ago. He does become tearful at times, particularly concerning his girl friend who comes from upstate to visit regularly each week. He does not want anyone to see him in this bad state, and that includes his mother, sister and girl friend as well. Dr. Jay stated that he has asked the patient why he is so irritable. The patient replies that people provoke him. Dr. Jay feels the patient is irritable because he is so scared. However, he is not irritable with Dr. Jay. Today the patient is too ill to be moved and interviewed in the conference room.

Conference Discussion

Dr. Sterling, an assistant resident, asked what has the patient been told. He knows that inconsistent stories have been told to the patient, not only on this admission, but on previous ones as well. The hematology fellow stated on his last admission that he should not be told anything. [Often, specialty groups dictate or try to dictate policy in patient care without discussing and agreeing with the housestaff on a consistent story.] Someone, on the other hand, told him about the results of his laboratory tests, which Dr. Sterling felt was rather inconsistent, since the patient had not been told the actual diagnosis. So a game goes on in which the patient is told all the details of his lab tests. Nothing is said about his illness and nothing is discussed about his feelings. The patient insists that he must know the results of every laboratory procedure. Now the test values reported to the patient are doubted by him.

It has been noticed that the patient's irritability increases when he receives poor laboratory figures and he must be aware he is going downhill. The patient knows, even before the platelet count is returned, that the platelets have been reduced. His gums get very sore and he also feels very weak from the decrease in hemoglobin. Therefore, no one can tell him that the lab values are good, when from his own physical condition, he knows that he feels poorly.

Dr. Zucker asked Dr. Jay his feelings about the patient. Dr. Jay said that he likes the patient and is touched by his plight. He also added that the patient's mother and sister, both feel very guilty about the patient. His sister feels that her divorce precipitated the father's heart attack, from which he died. Dr. Jay stated that he is deeply touched by the patient and Dr. Jay actually appeared to be on the verge of tears. To Dr. Zucker's question, he states he does not carry his feelings home with him. Dr. Zucker asked what can be offered to the patient's family. Dr. Jay replied that the best that could be done would be to sit and listen to them talk. To a mother, he feels that the loss of a child is an even worse blow than the loss of a husband. Dr. Zucker asked whether the mother has any strength. The mother relies a great deal on her daughter. The mother has been resisting the idea that the patient is critically ill and terminal, but more recently, from her questions, indicates that this awareness is increasing. She asked Dr. Jay whether the end for her son would be painful.

Dr. O'Brien, an intern, stated that she had been here during the summer when the patient achieved his last remission. At that time the patient was somewhat irritable with her. He wanted to know why the cephalin gave him a fever. Perhaps he was more upset than angry. Another incident occurred in connection with the previous period of hospitalization which must have disturbed the patient. Dr. Weiss, the chief resident, stated that after that second remission, which presumably would last for a period of three months, the patient expressed the wish to go to Europe. Instead, he was urged by the hematology group to remain in New York to be followed in the clinic. The patient was angry about this. On the other hand, it might have been that the patient was actually scared to go and was using the order from the hematology clinic as a rationalization. A third possibility might have been that the patient may have been misled by the hematology group who only suggested that he should remain in this country until his condition became more stable. Perhaps the patient did not want to assume responsibility for the decision which, indeed, would have been quite a burden. Dr. Weiss continued by stating that the patient has developed a real attachment to the hospital. After his last discharge he visited the ward on an average of once a week. He was particularly attached to Dr. Weiss' wife who, during his first admission, was a medical intern on the ward.

In continuing the discussion about the patients present management, Dr. Berg, the other assistant resident, stated that the housestaff does not want to tell the patient he is going to die in a week. Another housestaff member doubted that the patient obtained any relief in talking to the housestaff about himself. Dr. Jay stated that the patient wants to talk to the psychiatrist. Dr. Berg commented that too many people are talking to the patient already, which includes various members of the house and attending staffs and the hematology group as well. Nevertheless, he too feels that the patient wants somebody to talk to. Dr. Jay stated that he tries to encourage the patient to talk. Dr. Sterling said he finds it very difficult to talk to a dying boy his own age.

The chief resident commented that this is a frightening disease to everyone. When he was an intern they had many patients on the ward dying of leukemia. He washed his hands 40 to 50 times a day because leukemia is apparently a viral disease, hence, perhaps, indicative of infectious etiology. Fear on the part of the doctors he believes is rational but panic is not. At one time they had approximately 10–15 patients from Middletown, New York. He and others felt that this was a significant cluster, although other doctors, including those from the Public Health Service, felt it was not. At this moment, there was a general hubbub, in which at least half a dozen members of the housestaff were speaking simultaneously.

Dr. Zucker asked Dr. Stan to explain how he became involved in the case. Dr. Stan stated that he had made rounds Monday with the staff, who were having difficulty in dealing with the patient. Various suggestions were made at that time. Should the patient be morphinized and put into a twilight state or, as somebody jokingly said, "Perhaps we should get him a girl." Someone else suggested that he be given LSD. Another suggestion was that the staff should try to find out from the patient what he most wanted and give it to him. Lastly, it was suggested that someone talk to the patient about his fears and concerns, but at this point a pass-the-buck attitude developed in which no one seemed willing to approach the patient. No one wanted to commit himself. And yet, said Dr. Stan, everyone in medicine has to face the dying patient.

Dr. Jay stated that he fears that if some one talks to the patient, the patient's defenses will be broken down. If that happens the doctor-patient relationship cannot be maintained. He feels it is better to support the present charade of the doctor-patient relationship. Dr. Weiss stated that the patient would feel more comfortable if he knows that the doctors are treating him as a patient. If a doctor adopts any other attitude, such as a friendly one, the doctor loses his authority. [By this time the liaison psychiatrist was angry at the chief resident for not responding to the patient's needs.] Dr. Charles stated that everyone is caught up in their own feelings toward the patient. Dr. Berg stated that it does serve a function to talk to the patients about laboratory tests. Again at this point there were more than a few people speaking simultaneously, very much like a discordant sextet, in which each was expressing his own thoughts and feelings. Dr. Skinner joined in by asking why the doctor could not talk as a doctor to the patient about laboratory tests and talk to the patient as a person as well. Dr. Zucker took up this theme and asked whether the doctor can play two roles. The first role would be business as usual and the second role would be adopting a closer or more feeling attitude toward the patient. Would this reassure or terrify the patient? Would a change in the doctor's previous behavior frighten the patient? Dr. Zucker commented that it seems that Dr. Jay does not want the doctor to adopt both roles. Whereupon Dr. Zucker asked what else might the patient fear. There was no response. Dr. Zucker asked the house staff how they would respond if the patient states that he is afraid of dying. Dr. Jay stated that the patient wants reassurance that he is not. Dr. Berg stated that psychiatrists do not do the physical examination on their patients. The same thing should hold true in reverse as far as the intern is concerned, meaning that he should not do psychotherapy on his patients. Dr. Sterling stated that he feels that the doctor's acting as a friend to the patient would disrupt the entire relationship. The doctor's emotional distance from the patient would then be lost. The emotional distance he feels is there because the doctor, too, is scared. And again he reiterated his main point that the doctor as friend could not maintain his position as doctor. Dr. Zucker asked them to recall that the psychiatrist, too, is a doctor. To this Dr. Jay stated that to a layman, the psychiatrist is someone to talk to, and doctors, i.e., internists, prescribe medicine. Again Dr. Jay felt that the patient needs an outsider as a confidant.

Dr. Charles then referred to Dr. Cecily Saunders, whom he had met when he was a Yale medical student. From observations of her work with dying patients it became clear that patients did not have to be isolated from doctors. Also, if the family was involved with the patient, the patient's agitation and fear decreased.

Dr. Jay again stated that there should be a third party to do the talking with the patient. Dr. Zucker felt that Dr. Jay was shifting his position from his previous statement. He now seemed to be saying that the third party should help in initiating a dialogue. Dr. Zucker then commented that we are trying to deal at this moment with the doctor's anxiety. How many doctors can deal with their own anxiety? To young doctors, dying is done only by older people. He then asked, "What would you do if you were told that you would be dead in three months?" Dr. Berg stated that he would be angry, fearful, depressed, and probably suicidal. Dr. Zucker commented that the doctor's fear is that he will be haunted by the patient and in some way forced to tell the truth in a way the doctor does not want to say it. The chief resident asked how then can you communicate with the patient? Dr. Zucker suggested that he would approach the patient by telling him that he appears to be quite frightened. Dr. Jay stated that this patient denies that he is frightened. Dr. Zucker continued with his previous point that this would be a good approach with this patient. The patient might reach out for reassurance even by holding the doctor's hand. To this Dr. Weiss states that he would never get himself into such a situation. He would lie and lie to the patient. Dr. Stan stated that he wonders whether the immediate question that the patient would ask, actually would be, is he going to die. Dr. Berg said that if he were caught he would have to tell the patient, to which Dr. Zucker said, "but in a way that the patient couldn't possibly accept," i.e., by telling the patient that he has only a certain number of weeks or days to live. Dr. Stan responded to his own question by stating, that if the patient posed this question to him, he would not answer it. He would ask the patient about his fears and concerns. Dr. Weiss said that if the patient is going to die, what can be told him? Dr. Zucker said that Dr. Weiss assumes that he knows what is troubling the patient, but actually does not know, since he has not asked. Dr. Berg commented on his experiences as an intern when he had some sixty patients who were about to die. He said only one patient took it calmly. Most patients, when told they had a fatal illness, said that the doctor was lying and refused to believe the doctor.

Dr. Charles stated that Dr. Saunders never actually tells the patient anything. She talks with the patient about other things. Dr. Zucker said that the group seemed to be circling around the question of whether there is hope for life, life in the world of reality or in the hereafter. He quoted a fragment of Dr. Roose's paper in which Dr. Roose told his patient that he knew nothing about death, that he could only help him with living (6). Fear, such as this patient has, interferes with living. He cannot effectively use what is offered to sustain life or at least make it comfortable. If he is helped to relieve his fear, what is left of his life would be better.

Dr. Poland asked, "Who are we dealing with—are we dealing with ourselves or are we dealing with the patient?" Dr. Weiss said, "What about treatment for his pain?" Dr. Zucker stated that the patient's pain from the abscess of his hand is another matter in comparison with the pain due to anxiety and fear. How much is his anxiety and depression being helped? Are we treating the doctor or the patient? Dr. Jay said he would not use morphine. That would mean that we are giving up and also letting the patient know we are giving up.

At this point Dr. Zucker stated that the session was running overtime. Dr. Weiss immediately responded by saying this was an important problem and someone else in the background added that they could take a half hour for lunch today. Dr. Zucker felt that the doctors of this patient are afraid of letting him give up. Dr. Zucker then referred to his experience as a general practitioner with a 90-year-old patient. After an illness from which she recovered this patient reproached him for keeping her alive. She remarked that something in her would not let her die. As a matter of fact, she died several months later for other reasons. Dr. Jay said, therefore, he is against the use of morphine. Dr. Zucker directed his next comment to Dr. Poland. Can the patient be helped to give up? What about the patient's guilt in connection with his angry feelings? Is he guilty about abandoning his mother, sister and girl friend, and also angry with them all? The patient has not had a chance to ventilate this anger and hence relieve the guilt stemming from it. He asked then whether Dr. Stan had anything to add. To this Dr. Jay responded by saying, it is not a matter of adding anything, we haven't started yet. Dr. Stan stated that the patient does not make it easy for anyone to communicate with him. As a doctor, he would listen and the patient eventually would give him an opening if the doctor stayed with him long enough. [Dr. Zucker's original goal was to help these potential internists deal directly with such a patient. As the conference proceeded he became aware that he was asking too much of these young men to carry this burden themselves. He changed his goal solely to getting permission for Dr. Stan to see the patient.]

Dr. Zucker stated that this matter appears to be more than the staff can face at this time in their lives. Dr. Jay said that it is easy for the psychiatrist to step into the picture, because he, unlike the housestaff, does not have to see the patient every day and watch him die. Dr. Berg disagreed by stating that the psychiatrist should be in the picture because he has more training. Dr. Zucker said that the psychiatrist indeed may have more training and be better able to cope with such a patient. He acknowledged Dr. Jay's reaction that, of course, the psychiatrist is not in constant contact and does not have to be faced with the patient throughout the entire day, day after day. To this Dr. Jay again commented that he and other doctors have to watch the patient die. Dr. Weiss added, "As if he is laid out on a bier now."

Dr. Zucker tried to pick up the thread by agreeing that it must be painful to have to watch the patient die. Perhaps, the doctors wish that his death would occur more quickly. Feelings in the doctors are much more intense than feelings of someone who is not as close to the patient. So the wish would be that the patient die so they wouldn't have to look at him everyday. Dr. Jay disagreed somewhat, he would like to think more positively. He would like to see the patient walk out of the hospital on his own two feet. He has not yet seen many dying patients. Perhaps in this way he tries to deny to himself his reactions to death. Dr. Weiss stated that it is hard for the psychiatrist, too. Dr. Zucker wondered what he meant. Dr. Weiss explained that he meant, that the psychiatrist, too, does not have any answers. Dr. Berg stated that this is only true to the extent that the doctor does not have an A, B, C, D, E carefully mapped out. Several members of the house staff agreed that indeed there is no plan of any kind.

Dr. Zucker asked the house staff, would they agree to let Dr. Stan talk to the patient. None of the house staff said no. Dr. Poland stated that, with imminent death, the patient needs chemical assistance more than he does being talked to. Dr. Weiss said he is seriously considering morphinizing the patient. Dr. Berg said you can talk just so much to the patient. Dr. Poland stated that maybe the patient fears death will be very painful. Dr. Zucker said that he can understand why Dr. Weiss wants to do something, and apparently cannot listen to Dr. Jay's suggestion. In any case, at this time the patient has not complained of any physical pain. Dr. Weiss said that he is not trying euthanasia or trying to kill the patient. There was a chorus of responses from several members of the house staff, who said, "Oh, yes, you are".

Dr. Berg proposed that the patient be given morphine and be talked to as well. Dr. Zucker said that if Dr. Stan can help the patient in any way, he should take careful note of his communications with the patient. Dr. Weiss asked that the psychiatrist present a protocol. Dr. Zucker said that the chief resident was angry at him, to which the latter objected. Dr. Zucker continued by stating that there can be no set program. Every patient's needs are different. One must offer hope on the patient's terms. Dr. Weiss said that every time a conference is concerned with a leukemia patient, everybody argues, but nothing is done and the patient suffers. Dr. Poland states that he wants to treat the patient immediately. Dr. Zucker reiterated his previous request that he would like a psychiatrist to be given some time with the patient. Dr. Weiss said he is not being hostile; other members of the housestaff disagreed with him. Dr. Zucker stated that perhaps Dr. Weiss is angry because he cannot control the patient's pain and is angry because no one can save his life. Dr. Berg said that maybe offering the patient ten minutes of talking might make him feel good. Dr. Zucker asked, "Well, are we agreed that Dr. Stan is to see the patient?" Dr. Weiss said, "All right, you can see the patient if he's alive, but I warn you now that he won't be alive when you come back from lunch." Dr. Berg responded that he definitely knows that morphine, in comparison to talking, can make the patient feel good. Dr. Zucker commented that morphine would only increase the patient's difficulties.

The unit social worker stated that she had had contact with the patient previously and noticed how anxious he was. Dr. Zucker, in response to her comment, referred to Dr. Jay's previous remark indicating that the patient does want to talk to a psychiatrist. Dr. Weiss stated that the patient has given up. Dr. Zucker replied that we all hate to see him give up.

After the session Dr. Zucker commented, that to him it seemed that Dr. Poland was near tears. Dr. Roose could not see Dr. Poland's face during the conference, but could observe Dr. Jay's face and it was a most troubled expression. After the conference, Dr. Roose, Dr. Zucker, Dr. Stan and Dr. Alman had lunch together. Dr. Roose commented that only now was he aware of a tight feeling in the pit of his stomach. Dr. Zucker nodded and smiled. Dr. Stan returned after lunch to see the patient who began to ventilate his anxiety. They established an excellent relationship. For the remainder of the patient's stay there were no severe behavior problems. The patient went on to state that he did have thoughts about dying but he hoped that death would occur when he was 25 years old—three years from that time. His denial appeared to be working effectively. He asked if Dr. Stan would return to see him.

In speaking to each member of the housestaff later, Dr. Stan stated that morphine was contraindicated. Dr. Jay said he would shoot anyone who ordered morphine. Several residents shrugged and appeared unconcerned. Dr. Weiss said, "I'm glad you told me. I'll use this information the same way we use a lab test, but let me tell you, if he would have said he's afraid of dying I would have given him morphine no matter what you said."

That interview marked the beginning of a relationship between Dr. Stan and the patient which lasted eight months until his death. The patient achieved a state of incomplete remission and was discharged in several months time. They continued meeting when the patient returned to the OPD and during the patient's final rehospitalization.

Discussion

No attempt was made to identify all of the factors which made the housestaff so vulnerable to this particular patient's situation. One definite factor was the patient's nearness in age; speculation about the other factors would be useless. A point by point analysis of the feelings of the housestaff is unnecessary. It is enough to say that many intense feelings were revealed which clearly indicated the degree of dissension among members of the staff and the conflicting feelings within the individual doctors. If the detailed presentation of the liaison conference leaves the reader with a sense of confusion about what actually transpired, who said what and why, then the inability of the housestaff to cope effectively with the patient in the face of the swirling intensity of their contradictory feelings, is accurately reflected. It is as if the housestaff stated to the patient, "You are making us very anxious and we are angry that you do that to us."

Identification with the patient evoked a wide variation of reactions ranging from tears to anger, from compassion to withdrawal. Most striking was the ultimate common reaction that no housestaff member could speak to the patient to establish communication with him which he so desperately needed. The young psychiatric resident was less anxious and less contradictory in his plan of treatment. Dr. Zucker was fully aware of his own anxiety and, during one phase of the conference, of his anger. At that point recognition of his own feelings led to a change in direction: let the psychiatrist handle the patient rather than be led into a futile impasse with the housestaff and continued abandonment of the patient. The doctor who is unduly anxious cannot tolerate the anxiety of his patient. His very human reaction is to protect himself, but at the cost of abandoning the patient. Tears or anger are unacceptable inducements to the patient to express clearly his own feelings. For the dying patient, the helpful physician is one who has the inner strength to cope effectively with his own anxieties, consciously or unconsciously, who is able to listen, accept what is said, say little, interpret nothing, protect the patient from frightening reactions of staff or family, and to remain with the patient for as long as he lives. The only wishes this patient expressed were that the psychiatrist return tomorrow and that he become interested in his experiences, fears and hopes. Surely these were not exorbitant demands on a doctor's therapeutic resources.

The liaison psychiatrist is often confronted with the question of who is more anxious, the patient or his physician(s). Not infrequently he finds that the younger doctors on his service are having difficulty in coping with their anxiety and are overtly reacting with emotional isolation, suppression, denial, physical avoidance, and anger, usually covert and rationalized. The defensive maneuvers of the housestaff all too frequently find support in the model set by the senior attending physicians who, in their housestaff days, had no psychiatric liaison support. The social structure of the teaching hospital with division of function, particularly the delegation of family contact to social workers, the absorption of staff in academic and research responsibilities and the rapid rotation of attendings and housestaff offers a realistic structure which fosters rationalizations for the avoidance of anxiety-provoking patients both by attendings and housestaff. As a result the patient is often confronted by an impenetrable facade of distance and withdrawal.

The liaison psychiatrist is not immune to anxiety generated by a patient's character and life situation, but the early recognition of affects and defenses mobilized within him will usually permit him to be more effective in patient-directed (rather than disease-oriented) therapeutic efforts.

The efforts of the liaison psychiatrist must also be directed to the housestaff in order both to facilitate comprehensive care and to educate the future attendings. The housestaff need to ventilate their feelings and be supported rather than forced into closer patient contact than they can tolerate at the moment. They can be helped to assume increasing responsibility, limited only by the individual doctor's character structure. This is a learning process which should begin in medical school and should be carried on throughout the doctor's professional career. It is a process of increasing self-awareness of one's emotional makeup so that the doctor, like all effective health care workers, professional and paraprofessional, can use his feelings to relieve pain and suffering.

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The Lung in Systemic Lupus Erythematosus: A Clinico-Pathologic Study of 20 Cases

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Abstract

The pulmonary lesions in 20 autopsied cases of systemic lupus erythematosus are described. The most frequent finding was interstitial pneumonitis. Other lesions commonly encountered were pleurisy, with or without pleural effusion, atelectasis, and bronchopneumonia. Acute and chronic changes of the pulmonary vasculature were prominent. The correlation between clinical and pathologic findings was poor. Primary pulmonary involvement in SLE is common, however, the changes may be obscured by congestive heart failure, secondary infections, and uremia.

A variety of pulmonary lesions have been described in systemic lupus erythematosus (SLE) since Osler described a case of SLE with prolonged consolidation of the left lower lobe (1). Subsequent investigators have confirmed the frequency of pleurisy and pneumonia in SLE (2–4). These changes were initially regarded as a result of secondary bacterial infections, but the possibility of primary pulmonary involvement in SLE was also considered. Focal atelectasis in the lungs of patients with SLE is well described (2, 3). Aitchison and Williams noted widespread degeneration and fibrous changes in small pulmonary vessels in one of their three patients (5). Purnell et al found a variety of nonspecific pulmonary changes in the 54 patients they described (6). They described basophilic mucinous edema of perivascular and peribronchial connective tissue and of the alveolar walls but found no pathognomonic lesions. They concluded that the pulmonary lesions in patients with SLE were due to secondary infection and vascular damage. Hematoxylin bodies were found in the lung of one of the 12 patients studied by Olsen and Lever (7).

The inconsistency of the described pulmonary findings in SLE prompted the present investigations.

Materials and Methods

A review of the autopsy files of The Mount Sinai Hospital disclosed 20 cases from 1963–1973. The diagnosis had been confirmed by the typical clinical and laboratory findings and the LE phenomenon had been documented in all cases. Characteristic skin lesions had been seen in 19 cases. The clinical records were reviewed and certain features were critically evaluated: mode of presentation of disease, time of onset and symptoms of respiratory involvement, duration of disease, and cause of death.

Paraffin sections of pulmonary tissue (4–5 in each case) were stained with

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Hematoxylin and Eosin, elastica van Giesson and, when indicated, Masson's trichrome. Some sections were subjected to the Periodic Acid Schiff (PAS) reaction.

Results

Clinical studies

The patients, all women, ranged in age from 16 to 67 years with an average of 37 years. The duration of survival from diagnosis to death was one month to 20 years, with an average of 6½ years. Most patients presented with polyarthritis, fever and a typical butterfly rash. The laboratory findings invariably included positive LE cell preparations and positive anti-nuclear antibodies. They were treated for variable periods with adrenocortical steroids. A few patients received Immuran® and cyclophosphamide. Renal failure and congestive heart failure, were treated in the standard ways, whenever they occurred.

Eight patients developed terminal renal failure; in six, hypertension was a clinical problem. Three patients died of septicemia (Pseudomonas and Enterococcus). Other causes of death were atherosclerotic cardiovascular disease with or without myocardial infarction, and acute myocardial infarction due to coronary arteritis. In one case an aneurysmal intrahepatic artery ruptured with intrahepatic bleeding. Diffuse small vessel thrombosis and pulmonary infarction caused the death of two patients. Metabolic derangements, without any anatomically demonstrable lesion, were the causes of death in two other patients. The causes of death are summarized in Table I.

Respiratory symptoms and signs, prominent in six patients, were related to pleurisy and pleural effusion, bronchopneumonia, atelectasis, and pulmonary infarction. In one case moderate to severe dyspnea had been a clinical problem for many months prior to death without evidence for cardiac, respiratory, or renal disease. At autopsy the lungs showed vasculitis, fibrocellular intimal thickening of elastic arteries, muscular arteries with thickened walls and narrow lumina, and chronic interstitial inflammation and fibrosis, with organized pulmonary thrombi and foci of pulmonary infarction.

TABLE I

Causes of Death in 20 Cases of Systemic Lupus Erythematosus

Cause	Number of Cases
Renal failure and uremia	8
Septicemia	3
Atherosclerotic cardiovascular dis.	3
Acute myocardial infarction due to coronary arteritis	1
Rupture of intrahepatic artery	1
Generalized vessel thrombosis	1
Pulmonary infarction	1
Anatomically undetermined	2

Pathology

A variety of pathologic changes were noted in the lungs. The commonest lesion was alveolar septal thickening by inflammatory cells, particularly lymphocytes, plasma cells, and giant cells (Fig. 1). This thickening was extensive in 11 patients and was seen focally in an additional five patients. One case had moderate septal and intraalveolar pulmonary edema. In six patients the focal or diffuse interstitial inflammation was accompanied by variable degrees of septal fibrosis.

Bronchopneumonia was present in five patients. This was quite severe and extensive in one case, necrotizing in another, and focal in the remainder. It was associated with diffuse interstitial inflammation and prominent alveolar epithelial cells and with intracytoplasmic inclusions characteristic of cytomegalic inclusion body disease in one case. Intrapulmonary hemorrhage, occasionally with organization and alveolar cuboidal metaplasia, was noted. These lesions varied from a few subpleural petechial hemorrhages to extensive involvement of portions of lobes. Pulmonary infarction, recent and organizing, was found in three cases. Diffuse atelectasis occurred in one case and focal areas of collapse were seen in six others. Pleural effusion was common and generally bilateral. The volume of the effusion was as great as 1.5 liters in one instance. Seven cases had pleural fibrosis, two had fibrinopurulent pleural exudate, and one showed a fibrous pleuritis.

The walls of pulmonary arterioles were thickened, with almost complete

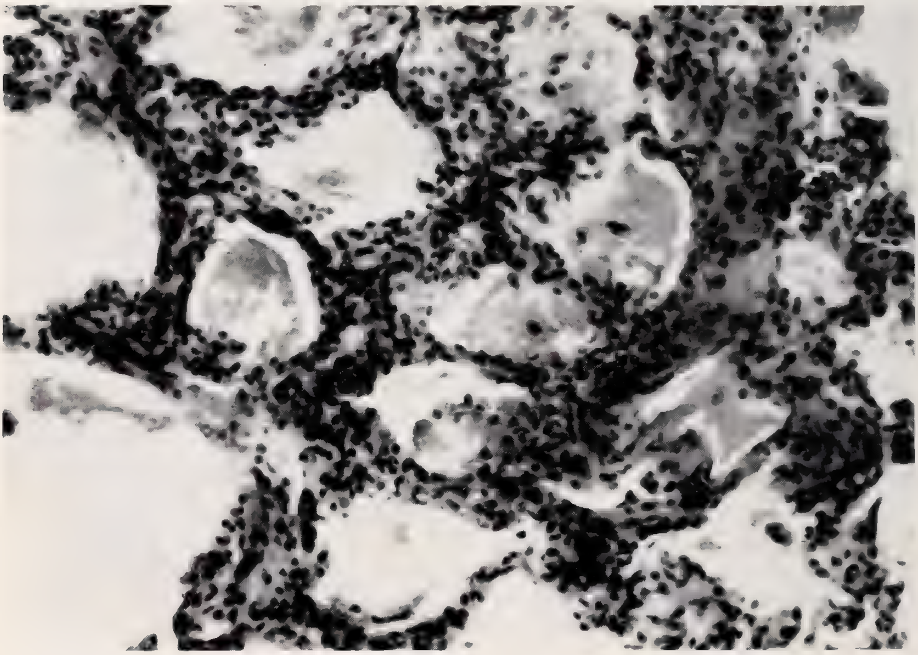

FIG. 1. Photomicrograph showing alveolar septa thickened by edema and chronic inflammatory cells. Alveolar spaces contain fibrin (H&E × 100).

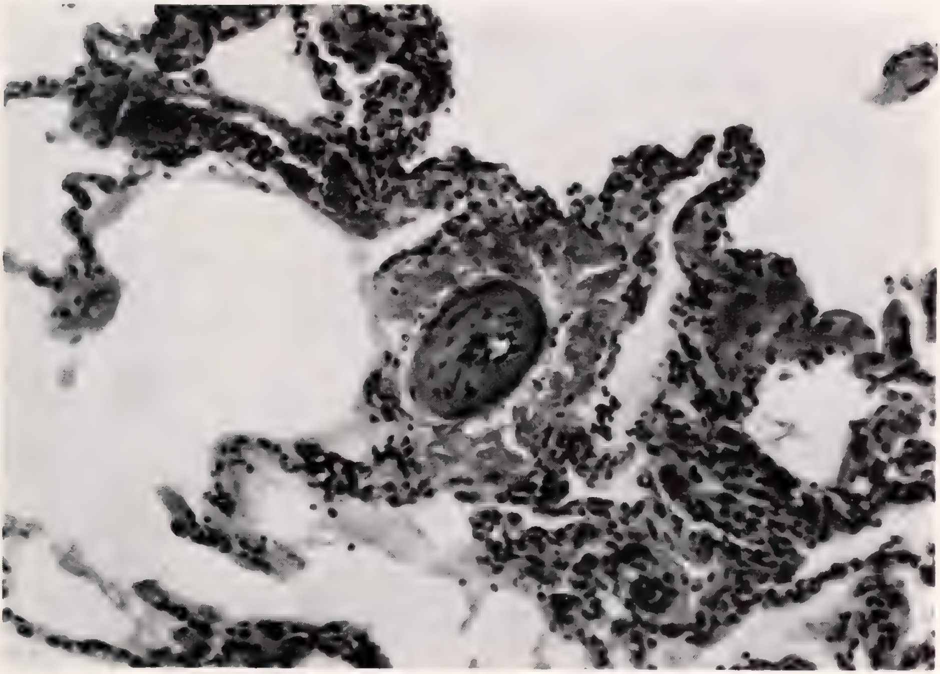

FIG. 2. Arteriole showing thickened wall and narrowed lumen. Note mild alveolar septal thickening (H&E × 100).

obliteration of the lumina (Fig. 2). Fibrinoid necrosis involved the entire wall of muscular pulmonary arteries (Fig. 3). Mild vasculitis and perivascular infiltration by lymphocytes was noted in many sections. The intima of muscular arteries showed severe cellular and fibrocollagenous thickening, with luminal narrowing (Fig. 4). The elastic tissue component of pulmonary vessels varied greatly. Medial hypertrophy was severe, and collagenosis of the media was rare. Thickening and reduplication, with occasional fragmentation and destruction, of the elastic laminae were noted (Fig. 5). There was moderate adventitial fibrosis (Fig. 6). One case showed perivascular edema. The elastic arteries showed mucinous degeneration of the intima and severe fibrocollagenous intimal thickening (Fig. 7).

Discussion

Three clinical patterns of pulmonary involvement have been described in SLE (8). The first characterized by pleurisy, usually bilateral, without large effusion, often associated with pericarditis, fever and toxemia. In the second there are recurrent febrile attacks of cough, with scanty sputum, pleurisy and dyspnea. This form responds to antibiotics. The third pattern is unexplained breathlessness, following and often punctuated by either of the first two patterns. Patients in this category improve considerably on corticosteroid therapy.

The present study confirms the multiplicity of the pulmonary lesions in SLE,

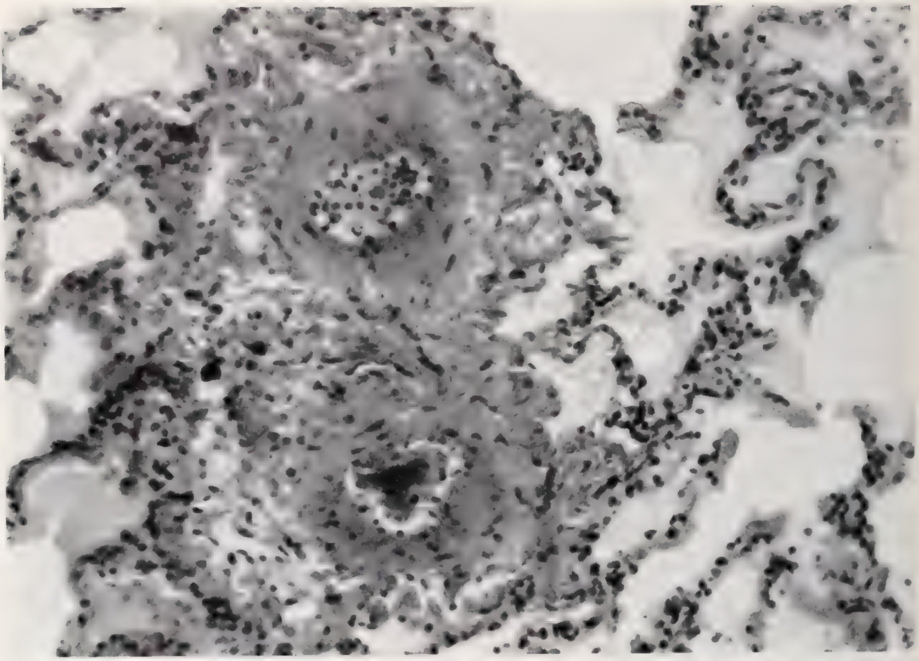

FIG. 3. Fibrinoid necrosis involving the wall of muscular arteries. Fragmented cells are seen within the necrotic wall (H&E × 100).

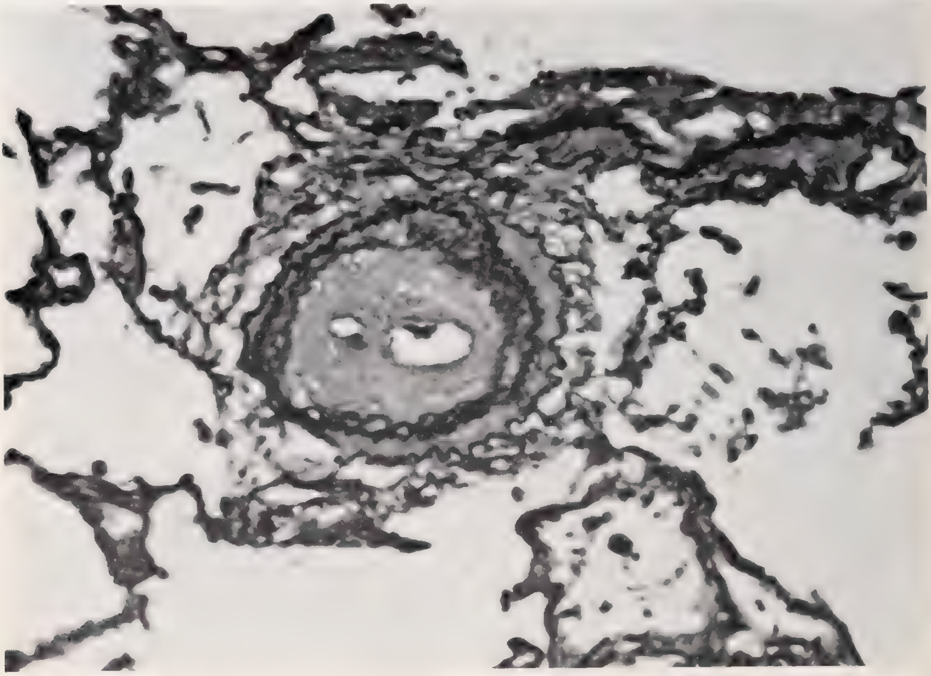

FIG. 4. Muscular artery showing severe fibrocollagenous intimal thickening and reduplication of internal elastic lamina (EVG × 100).

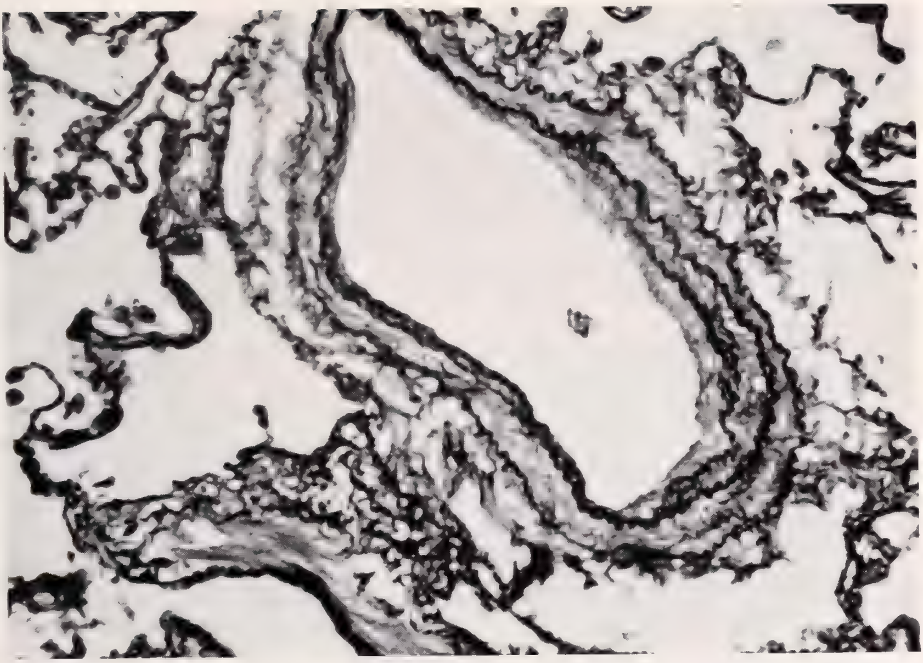

FIG. 5. Large muscular artery showing mild eccentric intimal thickening and prominent reduplication of internal elastic lamina (EVG × 100).

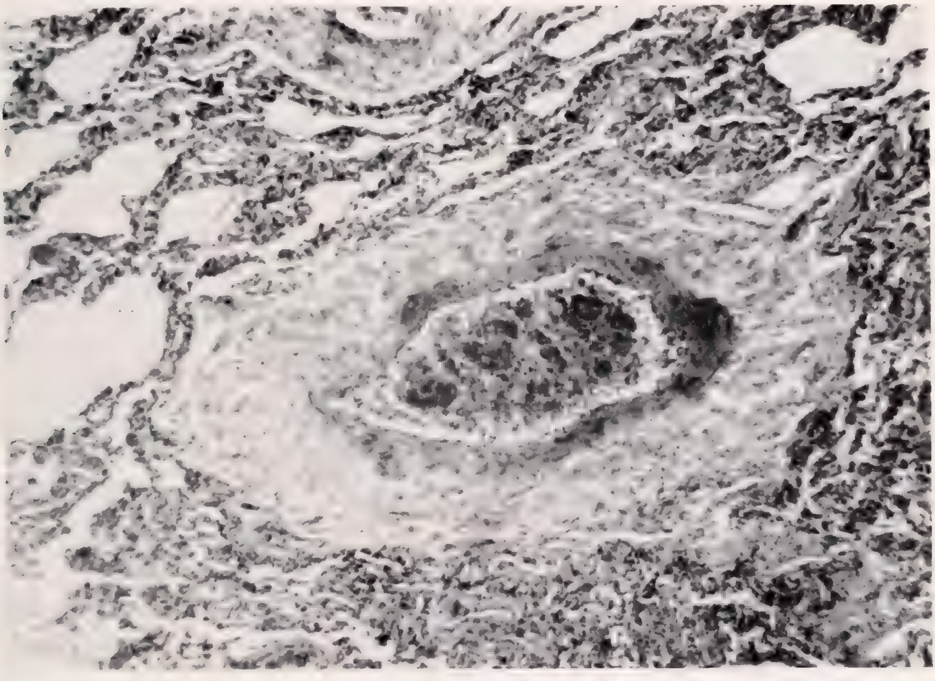

FIG. 6. Muscular artery showing adventitial fibrosis. The surrounding pulmonary parenchyma shows "atelectasizing pneumonitis" (H&E × 100).

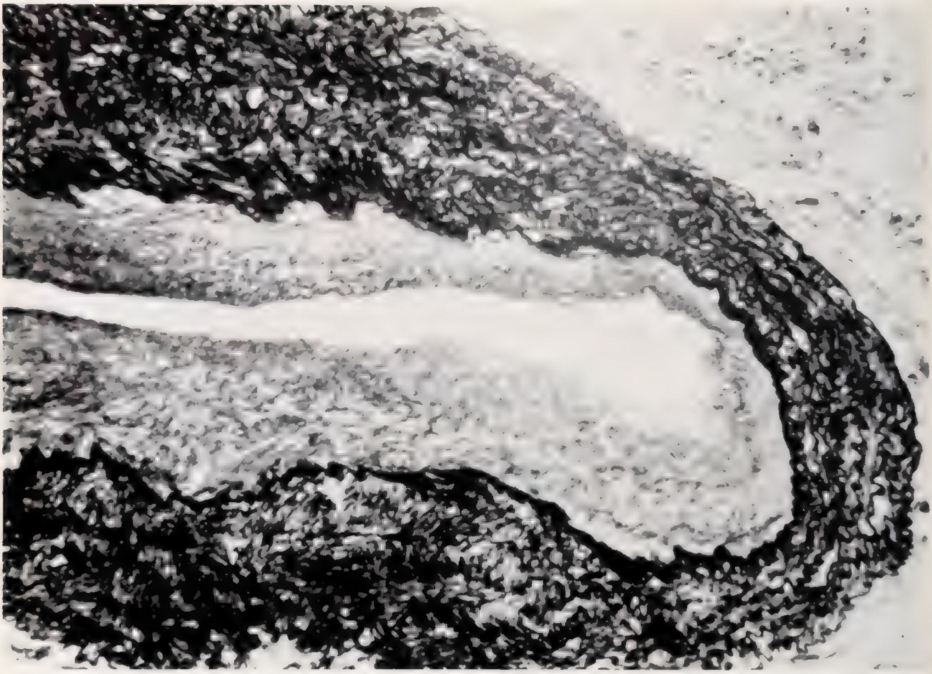

FIG. 7. Elastic artery in a 37-year-old patient showing severe fibrocollagenous intimal thickening and luminal narrowing (EVG × 100).

TABLE II

Pulmonary Findings Associated with Systemic Lupus Erythematosus

1. Recurrent and terminal bronchopneumonia*
2. Pleuritis, pleural effusion and pleural fibrosis*
3. Interstitial pneumonitis*
4. Pulmonary vascular disease:
    a. fibrinoid necrosis (11†)
    b. vasculitis (14†)
    c. perivascular mucinous edema (6)
    d. thickened arterioles and arteries (5, 11†)
    e. periadventitial fibrosis†
5. Atelectasis*
6. Miscellaneous lesions
    a. hematoxylin bodies (7)
    b. peribronchial and alveolar edema (6, 7)
    c. pulmonary fibrosis†

* Most authors.
† Present study.

most of which are nonspecific (Table II). Interstitial pneumonitis is the most frequent pulmonary lesion encountered. This finding is at variance with previous investigators who found that bronchopneumonia, pulmonary hemorrhage, and pleurisy with pleural effusion as the commonest lesions in SLE (4, 5, 9, 10). The susceptibility of patients with SLE to bronchopneumonia and pleurisy has been stressed. Klemperer et al (11) emphasized the occurrence of long bouts of "waxing and waning bronchopneumonia" as characteristic of this disease. Similar migratory pneumonic signs and symptoms were described by Osler (1). In this series five patients had bronchopneumonia and in all of these it was a terminal event. This susceptibility may be related to a general depression of resistance to infection, perhaps complicated by the alterations in bronchial and pulmonary vasculature.

Atelectasis in the presence of pleural effusion or in the absence of either bronchial obstruction or external compression of the lungs has been frequently described (10). The alveolar walls and the peribronchial and perivascular connective tissue show chronic inflammation which leads to obliteration of the alveolar spaces, for which reason some authors refer to an "atelectasizing pneumonitis" (12). It is associated with severe dyspnea and seems to offer an explanation for the clinical and physiological picture of shrinking lungs in SLE. It is believed that these changes may be important in clarifying some of the atypical pulmonary symptomatology in SLE (8).

Pulmonary vascular involvement in SLE has been reported less frequently than pulmonary parenchymal changes. Baehr et al found involvement of pulmonary vasculature in 23 autopsied cases of SLE. In four cases the right heart was enlarged. Three of the patients died of congestive cardiac failure. Klemperer described fibrinoid necrosis of pulmonary arterioles (11). Wagenvoort et al (14) reported a case of SLE with widespread necrotizing arteritis of pulmonary arteries and arterioles resulting in ischemic necrosis of large areas of the lung. Necrotizing pulmonary arteritis with subsequent fibrous occlusion of arterial lumen was found by Aitchison and Williams (5) in one of three cases of SLE. In the present study the vessels not only showed acute changes of fibrinoid necrosis and vasculitis, but also showed morphologic sequelae of healed or old vascular lesions, including intimal thickening, medial hypertrophy, alteration of elastic laminae, and adventitial fibrosis. These changes were widespread in eight of the 20 cases studied. No correlation was found between the type of pulmonary vascular lesion and either other associated pathologic findings in the lung or the duration of the disease.

These severe degenerative and fibrotic pulmonary vascular changes are similar to those found in other parts of the body, and are probably due to the involvement of the vessel walls by SLE. The obstruction to blood flow from arterial mural thickening may lead to pulmonary hypertension (15), hypertrophy of the right ventricle with eventual development of cor pulmonale. In spite of extensive vascular changes found in eight cases in this study, right ventricular hypertrophy or failure was not observed. Thrombosis of pulmonary blood vessels may follow vascular involvement and may result in focal infarction. This may be the basis of "unexplained breathlessness" described by Hoffbrand and Beck (8).

There are few studies of pulmonary function tests in SLE. Diffusing capacity may be impaired and vital capacity may be reduced. The former is attributed to increased membrane resistance associated with a restrictive pattern of respiration (interstitial edema, congestion, and inflammation) (9) and the latter to atelectasis (8). Radiologically, SLE often manifests as patchy pneumonitis, linear atelectasis and diffuse micronodular infiltration. Clinical and roentgenographic findings have not correlated well with abnormalities of pulmonary function. In contrast, physiologic abnormalities may closely reflect pathologic changes (9). The present study documents that pulmonary vascular lesions are common in SLE and may be an integral part of the disease process. However, secondary infection, uremia, and congestive heart failure may be overwhelming and may obscure vascular changes.

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Ischemic Colitis with Perforation into the Gallbladder

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Ischemic colitis presents a wide spectrum of clinical pictures ranging from transient ischemia to gangrene with perforation.

A 63-year-old woman presented with right-sided ischemic colitis and under conservative management developed a perforation from the hepatic flexure into the gall bladder without a dramatic change in the patient's clinical picture.

Case Report

A 63-year-old woman (SG#169498) was admitted to the Mount Sinai Hospital with a one day history of abdominal pain.

One day prior to admission the patient developed moderately severe, poorly localized right upper and right lower quadrant pain associated with nausea and shortness of breath. She had no history of gastrointestinal or biliary tract disease. She had a history of mild hypertension and shortness of breath for several years prior to admission.

On admission to the hospital her blood pressure was 100/75 mm Hg, pulse 140/minute, respirations 30/minute, and temperature 100.6°F.

Examination revealed an obese female in respiratory distress complaining of abdominal pain. Examination of the chest revealed fine basilar rales, a tachycardia and an S3 and S4 gallop. There was marked abdominal tenderness and guarding in the right upper and lower quadrants. The liver was enlarged to 5 cm below the costal margin and was tender. There were no masses palpable. There was guiac negative stool in the rectum.

Hemoglobin was 13.8 gm%, white blood cell count was 28,000, with a shift to the left. Urinalysis and serum chemistries were within normal limits except for a blood urea nitrogen of 39 mg%.

Chest X-ray showed prominent vascular markings. Abdominal films showed an ileus pattern. An electrocardiogram showed sinus tachycardia.

The admitting diagnosis was cholecystitis and congestive heart failure.

The patient was treated conservatively and responded to a regimen of N.P.O., intravenous fluids, nasogastric suction and antibiotics. The congestive heart failure improved and the patient's BUN returned to normal. An oral cholecystogram and an intravenous cholangiogram both failed to visualize the biliary tract despite a serum bilirubin of 0.6 mg%.

On the fourth hospital day the patient began to have diarrhea and 4+ guiac stools. She continued to have right-sided abdominal tenderness and guarding. A barium enema (Figs. 1, 2) was performed. From the cecum to the mid-transverse

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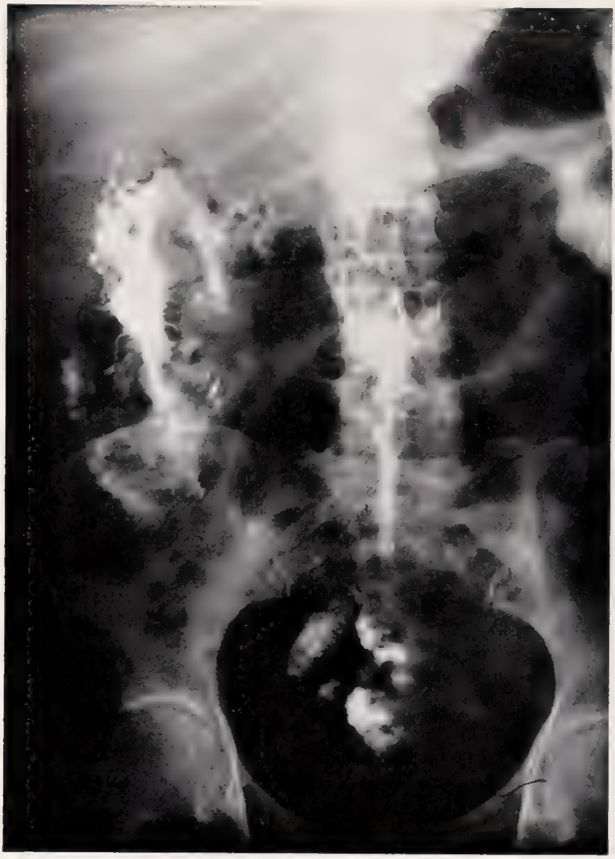

Fig. 1.

Figs. 1 and 2. Initial barium enema. From the cecum to the mid-transverse colon there is marked mucosal edema and "thumb-printing". Curvolinear lucencies rimming the colon in the hepatic flexure probably represent air in a submucosal location. There is no evidence of free air. An ileus pattern of the small bowel is present. The picture is consistent with ischemic colitis.

colon there was marked mucosal edema with "thumb-printing." In the hepatic flexure, curvo-linear lucencies rimming the colon were seen. These represented air in a submucosal location. The films are diagnostic of ischemic colitis involving the right colon.

Conservative management was continued. The patient developed gross rectal bleeding and transfusions were required. Gradually the patient responded. She tolerated a low residue diet and her stool became brown and guiac negative. Her abdominal signs, however, did not fully abate and she continued to have right sided guarding and tenderness.

A barium enema was repeated 3 weeks after the first study and it showed no loss of normal mucosa from the cecum to the transverse colon. There is narrowing but no stricture formation. A localized collection of air and barium is seen

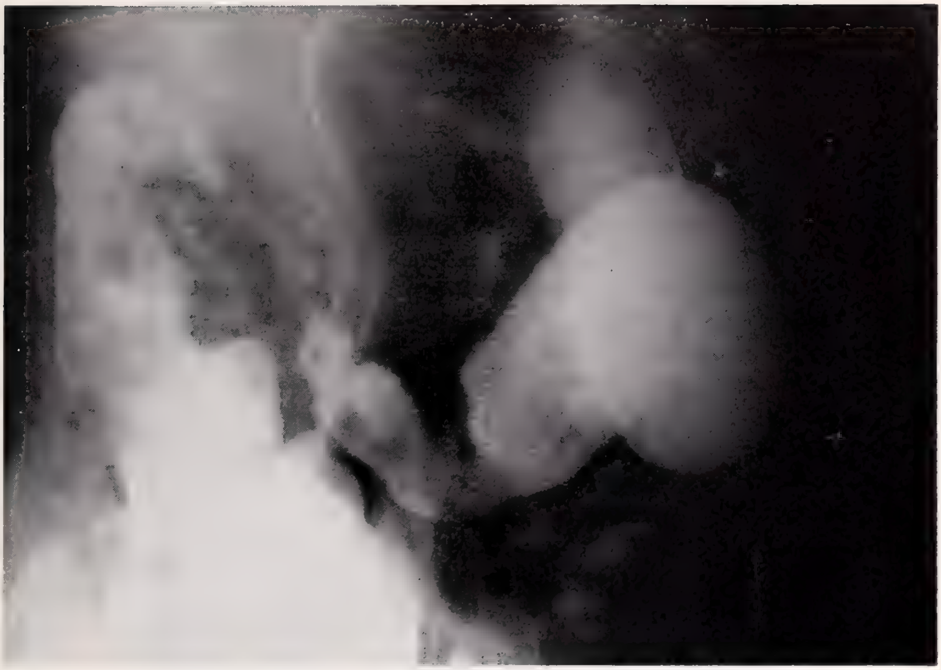

FIG. 2.

adjacent to the hepatic flexure in the right upper quadrant which represents barium in the gallbladder. (Figs. 3, 4)

A repeat OCG and IVC visualized the gall bladder and the biliary system which were felt to be normal. An upper gastrointestinal series, superior mesenteric angiogram and inferior mesenteric angiogram were normal.

Six weeks after the diagnosis of ischemic colitis was made the patient again spiked a temperature of 102°F and developed nausea, vomiting and abdominal pain. She again responded to conservative management.

A laparotomy was performed one week later. At laparotomy the colon appeared pale. A large, free perforation was present in the ascending colon just proximal to the hepatic flexure. The hepatic flexure was stenotic and nondistensible. A large abscess cavity filled the right upper quadrant, and communicated with the fundus of the gallbladder. The gallbladder contained barium, but no stones.

A right hemicolectomy and cholecystectomy were performed. Because the colon was pale and the blood supply to the remainder of the colon was uncertain, an ileosigmoidostomy was performed. The transverse colon was brought out over a rectal tube as a mucous fistula. Pathologic report was colon and gall bladder showing "acute and chronic inflammation."

The patient's postoperative course was unremarkable except for a wound infection that prolonged her hospitalization. She is now 4 months after surgery and

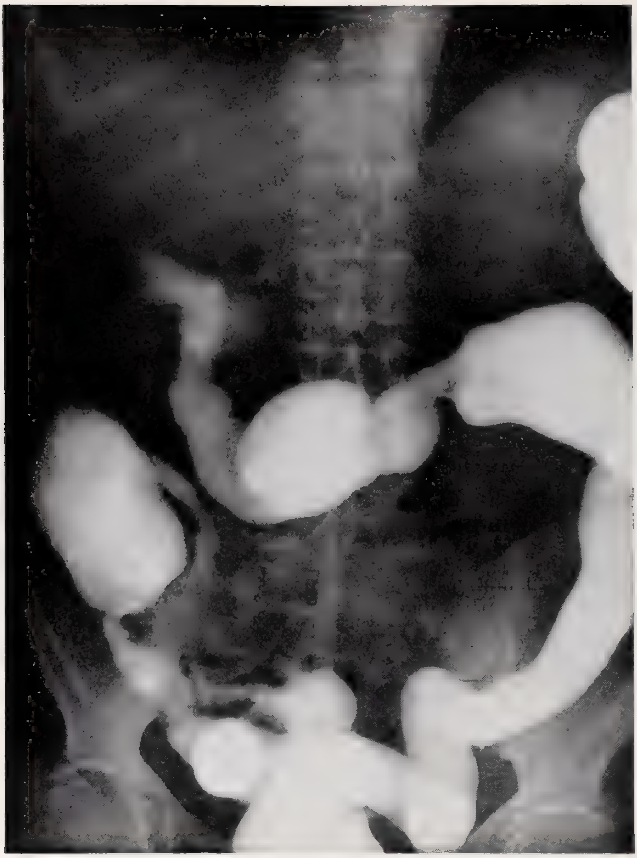

Fig. 3.

Figs. 3 and 4. Repeat barium enema. There is loss of the normal mucosal pattern from the cecum to the midtransverse colon. There is a smooth narrowing of the hepatic flexure which is only partially distensible. A localized collection of air and barium is seen adjacent to the hepatic flexure and appears to represent barium in the gall bladder. The picture is consistent with ischemic colitis with a colocholecystic fistula.

has no abdominal pain. She has about 4 semi-formed bowel movements per day and does not require medication for her bowels.

Discussion

The term "ischemic colitis" was first used by Marston (1) in 1966 to describe patients with vascular disease of the colon who had similar clinical, radiologic and pathologic findings.

The entity had been previously described under a variety of names including "infarction of the colon," "benign strictures of the colon," "reversible vascular occlusion of the colon," and "ischemic colopathy" (2).

Ischemic colitis may affect any segment of the colon. The most frequently involved sites are the splenic flexure, the descending colon and the sigmoid colon

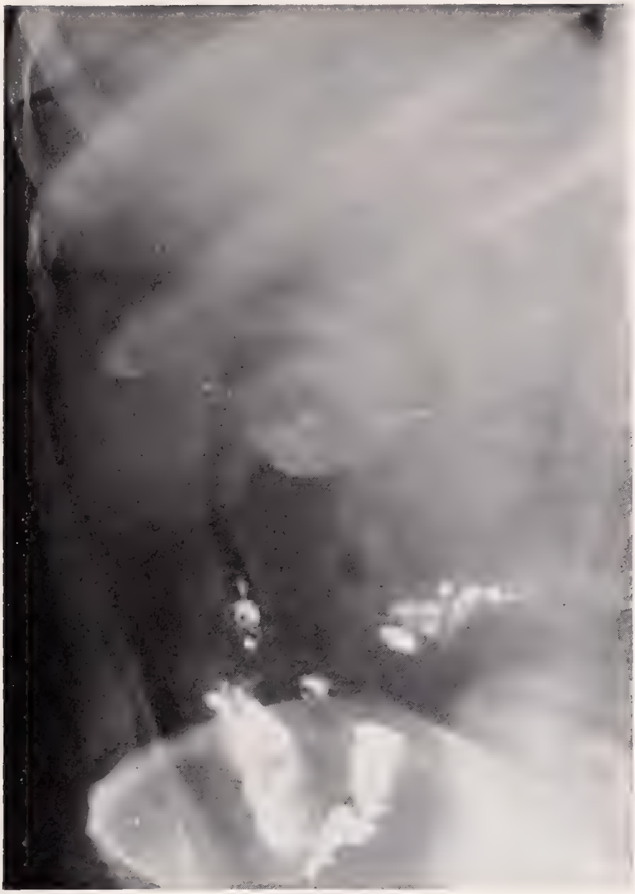

FIG. 4.

(2–4). Spontaneous ischemic proctitis has been reported (5). The right side of the colon is involved in about 10% of the cases (2–4).

Most patients are between 60–80 years of age, but patients in their 20's have been reported (2). Females outnumber males by 3:2 (2).

Arteriosclerotic narrowing of the orifices of the superior mesenteric artery and the inferior mesenteric artery is the most common cause of ischemic colitis (6, 7). Other causes of colonic arterial occlusion include hypercoagulable states as polycythemia vera, vascular diseases as lupus erythematosus and polyarteritis, and emboli to the bowel (7).

Well-defined arterial occlusion is not, however, always demonstrable. Angiographic demonstration of an acute occlusion is infrequent. Often there is considerable disparity between the degree of narrowing demonstrated and the ischemia present. Intimal hyperplasia may be noted in small mesenteric arteries with or without intestinal ischemia (7).

Low flow states may be associated with severe arteriole spasm and intestinal ischemia, and may be seen in patients with a pulmonary embolus, myocardial infarction, congestive heart failure, and arrhythmias associated with hypotension (7, 8).

The radiologic picture is diagnostic. The plain abdominal films may show segmental distribution of air in the colon with absent valvulae and haustral markings. Free air, intramural air, and gas in the portal vein are diagnostic of infarction (3).

Barium studies reveal spasm without proximal dilatation. The folds are thickened and blunted and "thumb-printing" is seen along the contour of the bowel. The entire mucosa may be denuded (3).

Barium studies in a later stage may show flattening and rigidity of the wall due to fibrosis. Sacculations or pseudo-diverticulae may be seen. A long tubular stricture may develop, but the stricture is usually shorter than the initial area of involvement (3).

Barium studies are usually unnecessary in ischemic colitis which results in gangrene of the bowel because perforation and peritonitis develop early. Because the ulcerations are usually shallow, sinus tracts and fistulas are unusual (3).

The clinical picture that develops in a patient with colonic ischemia depends on the etiology of the ischemia, the extent, rapidity and duration of the ischemia, the adequacy of the collateral circulation, and the extent and depth of involvement of the bowel wall (7).

Most patients present with an acute onset of intermittent pain spreading across the lower abdomen, often accompanied by nausea, vomiting, and the passage of blood per rectum (2).

When gangrene and perforation occur, it is almost always in the first 24 hours. Minimal ischemia resolves completely. The onset of anorexia, distention, constipation, and pain indicate stricture formation (2).

Marston described three possible courses for colonic ischemia:

1. Gangrenous ischemic colitis resulting from failure of arterial flow;

2. Stricturing ischemic colitis resulting from hemorrhagic infarction of the mucosa which is followed by fibrosis and stenosis; and

3. Transient ischemic colitis resulting from a mild transitory impairment of arterial supply and complete resolution (1).

Of 51 patients in a composite review, 4 patients had frank gangrene, 24 subsequently developed strictures and 23 were symptom-free after the ischemia resolved (2).

Once the diagnosis of ischemic colitis is established most patients can be managed safely with conservative treatment. The patient must be followed extremely closely for evidence of perforation or stricture formation.

The presenting symptoms of the patient in this report were those suggestive of biliary tract disease. The diagnosis was established only after she began to have diarrhea and guiac positive stools. The occurrence of right-sided ischemic colitis was unusual. The occurrence of congestive heart failure with low flow and intestinal ischemia may have been a precipitating factor. Superior mesenteric arteriogram did not reveal any vascular abnormality of the blood supply of the right side of the colon. The pathologic specimen did not show any microscopic abnormality of the small vessels of the colon.

The patient was managed conservatively, and responded initially, but was never completely free of pain or abdominal tenderness. The evidence of continuing disease should have suggested the possibility of an unsuspected perforation. Other patients with unsuspected perforations have been reported (9). In these patients and in the patient in this report the perforation occurred without any dramatic change in the patient's clinical picture.

The course of ischemic colitis is not predictable from a single barium enema. The clinical picture may be confusing. No single symptom or group of symptoms is reliable in predicting the outcome of ischemic colitis (9). A patient may have an ischemic stricture with no history of symptoms (10). Complete healing may occur despite severe involvement on initial studies (11). Cases of ischemic colitis of the right colon may be misdiagnosed as right-sided granulomatous colitis or ulcerative colitis, and may be more common than is reported (3).

The colocholecystic fistula that developed in this patient is a unique complication of ischemic colitis. It occurred without a dramatic change in her clinical picture and without cholangitis.

Because perforation of the colon is not always heralded by an abrupt change in the clinical status of the patient, a perforation of the colon should be suspected even in the absence of toxicity in patients with evidence of continuing disease.

Summary

A diagnosis of ischemic colitis was made on barium enema in a 63-year-old woman who presented with abdominal pain. She was treated conservatively, and responded initially, but not completely. Repeat barium enema revealed a perforation of the hepatic flexure of the colon into the gallbladder, a complication of ischemic colitis not previously reported. The perforation occurred without a dramatic change in the patient's clinical course, and without cholangitis.

The etiology and diagnosis of ischemic colitis are reviewed.

The failure of a patient with ischemic colitis to respond fully to conservative treatment should alert the physician to the possibility of an unsuspected perforation even in the absence of systemic toxicity.

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A Histologic Chronology of the Clinical Course of the Keratocarcinoma (So-Called Keratoacanthoma)

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Although the so-called keratoacanthoma is a relatively common skin neoplasm, having been described as long ago as 1888 (1), very little has been published with respect to the sequence of histologic changes that takes place from its inception to its involution or progression into a deeply invasive and or metastasizing squamous cell carcinoma (2–4). Indeed, after punctilious study of these histologic changes, combined with evidence of the clinical features of relatively large size, rapid growth, invasion, scarring, and well-documented cases of squamous cell carcinoma (5), some with metastases (6), developing from lesions formerly diagnosed as keratoacanthomas, I have come to the firm conclusion that all of these lesions are malignancies and that the formerly accepted concept of a self-healing primary squamous cell carcinoma of the skin (7, 8) is a correct one. Spontaneous resolution which occurs in a large percentage of cases is no proof of benignity, since the medical literature is replete with examples of well-documented malignancies of all sorts (9) which have undergone spontaneous regression. Therefore, I have termed this lesion a keratocarcinoma and shall refer to it as such during the remainder of this paper.

Materials and Methods

Skin biopsies of 159 solitary consecutive keratocarcinomas were collected for a period of one year (January 1, 1973 to January 1, 1974) from the files of the Skin and Mucous Membrane Biopsy Laboratory. There were no lesions of the palms, soles or mucous membranes. In each instance, the diagnosis was first established by a routine hematoxylin and eosin stain and then pursued by a careful clinical follow-up. In all cases, the clinician was advised either to completely remove or thoroughly destroy the lesion. In no instance has there been evidence of a recurrence or metastasis. The location of the lesions, sex and age distribution, size, and clinical course corresponded to what has been well-documented in the medical literature (2) and need not be detailed here.

Observations

Upon meticulous review and analysis of the clinical and histologic features of these keratocarcinomas, I have been able to reconstruct the sequence of microscopic changes that occurs during the course of this disease. Five distinct chronological stages could be distinguished—incipient (6% of cases), early (43% of cases), late (45% of cases), early involutionary (3% of cases) and late involution-

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TABLE I

Chronology of Keratocarcinoma

Stage	Incipient	Early	Late	Early Involutionary	Late Involutionary
Clinical appearance	Skin-colored or erythematous, firm keratotic papule or plaque	Skin-colored or erythematous, firm keratotic papule, plaque or nodule with or without a shallow, central keratin-filled depression	As early stage but with central, keratin-filled crateriform depression	As late stage but with flattening of borders of depression	Keratin filled cyst with large opening to surface
Other clinical impressions	Verruca vulgaris; seborrheic keratosis; actinic keratosis; various granulomas; metastatic cancer	As incipeint stage plus inverted follicular keratosis	Actinic keratosis; squamous cell carcinoma; basal cell carcinoma; giant molluscum contagiosum	As late stage	Giant comedo; keratinous cyst
Histologic differential diagnosis	Verruca vulgaris; seborrheic keratosis; inverted follicular keratosis; lichen planus	Lichen planus plus irritation of other lesions as in incipient stage	Squamous cell carcinoma arising from base of hypertrophic actinic keratosis	None	Keratinous cyst with scarring from prior irritation
Salient histologic features	Papillomatosis; hyperkeratosis; parakeratosis variable; hypergranulosis with prominent large keratohyaline granules; premature epidermal keratinization with "glassy-appearing" cytoplasms; proliferating basophilic rim; subepidermal vascular ectasia	A sincipient stage with or without a central, shallow keratin-filled depression plus invasion of papillary cutis by papillomatous proliferations of keratinizing cells having a rim of basophilic cells showing variable degrees of hyperchromatism, pleomorphism and mitotic activity with surrounding inflammatory cell infiltrate	As early stage but with crateriform depression and a variable degree of cellular atypism at base, often showing features of a squamous cell carcinoma; epidermal lip usually present	As late stage but with dissolution of atypical cells at base, disintegration of basophilic rim and papillomatous proliferations of keratinizing cells and exocytosis of wall of depression	Depression becomes shallow; epidermal lip recedes; wall of depression becomes flattened and atrophic showing normal maturation; maturing scar of variable depth beneath depression; loss of inflammatory cell infiltrate; finally a depressed scar with or without an epidermal lip

ary (3% of cases). Because of considerable variation in growth rates, it was not found possible to determine time periods for the various stages. The data are summarized in Table I.

The incipient stage keratocarcinoma is a slightly elevated, papillomatous, hyperkeratotic erythematous or skin-colored papule or plaque. Histologically (Figs. 1A and 1B), one observes a mildly papillomatous lesion covered by an epidermis showing variable degrees of hyperkeratosis, hypergranulosis, acanthosis and premature keratinization. The latter is characterized by enlarged cells of the lower portion of the malphigian layer associated with abundant eosinophilic glassy appearing keratinized cytoplasms and most often a thick granular layer with prominent, relatively large keratohyaline granules. Parakeratosis is inconstant and may be absent, minimal or conspicuous. There is no inflammatory cell infiltrate at the dermal-epidermal junction. Mitotic activity is increased within and about the basal layer, often appearing as a prominent rim of proliferating basophilic cells of variable thickness. The PAS stain shows a well-defined and intact basement membrane zone. At a slightly later incipient stage (Figs. 2A and 2B), one observes an exaggeration of all of these changes. There may or may not be a shallow central depression and vascular ectasia is prominent within the subepidermal zone. The early stage is ushered in shortly by the advent of invasion beyond the basement membrane zone (Figs. 3A and

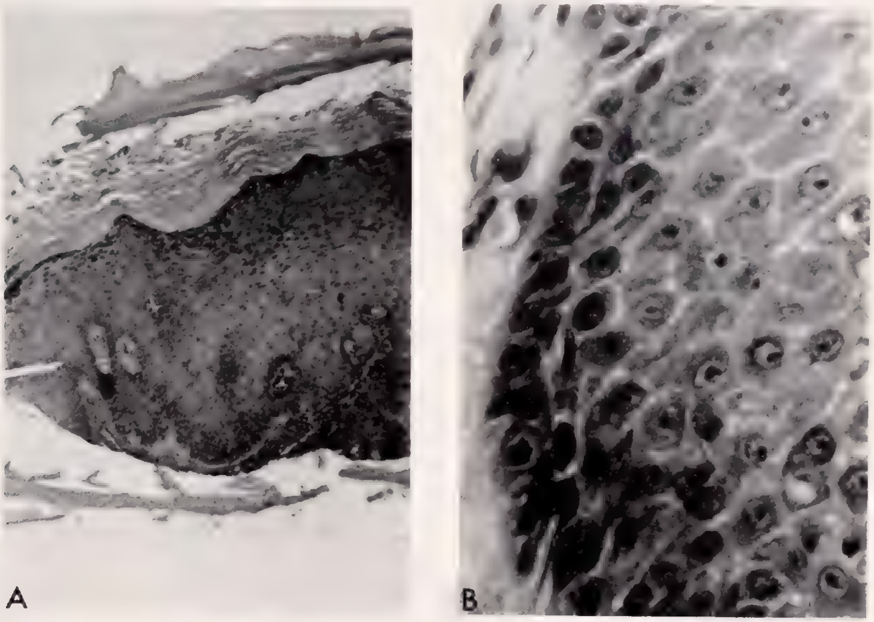

FIG. 1A. Incipient stage showing mildly papillomatous epidermis, hyperkeratosis, hypergranulosis, acanthosis with premature keratinization and absence of inflammatory cell infiltrate at dermal-epidermal junction (hematoxylin-eosin × 40).

FIG. 1B. Higher magnification of base of Fig. 1A demonstrating premature keratinization, proliferating rim of basophilic cells and absence of inflammatory cell infiltrate at dermal-epidermal junction (hematoxylin-eosin × 400).

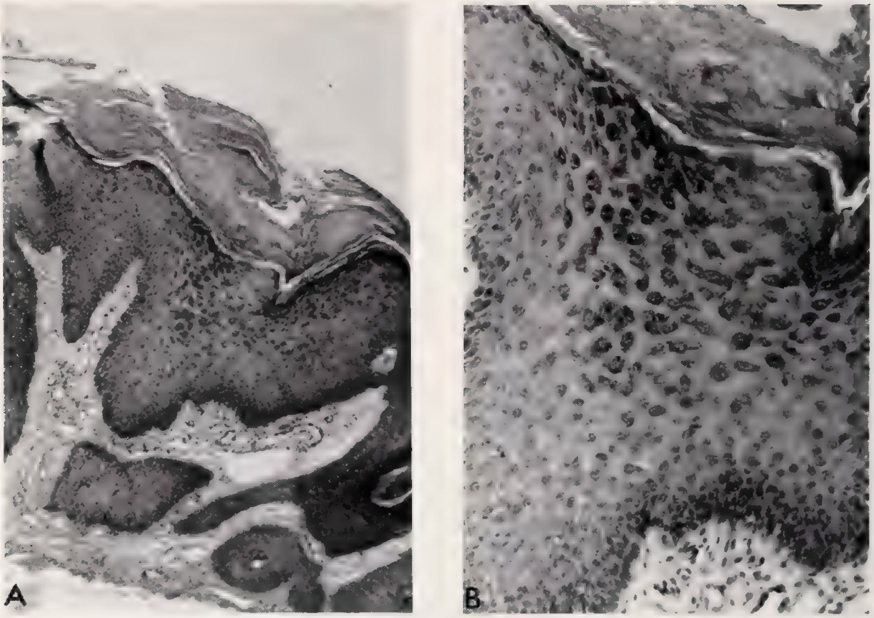

FIG. 2A. A slightly later incipient stage than that depicted in Fig. 1A showing similar but more advanced changes with beginning crater formation and ectasia of blood vessels in papillary cutis (hematoxylin-eosin × 40).

FIG. 2B. Higher magnification of Fig. 2A emphasizing prominent rim of proliferating basophilic cells, "glassy appearing" cells in malpighian layer and hypergranulosis with large prominent keratohyaline granules (hematoxylin-eosin × 100).

3B). At this stage, the most striking additional features are those of dermal invasion by papillomatous proliferations of keratinizing cells surrounded by a rim of basophilic cells showing variable degrees of nuclear hyperchromatism, pleomorphism and mitotic activity and an inflammatory cell infiltrate (consisting mainly of lymphocytes, histiocytes and neutrophils) associated with edema at the dermal-epidermal junction, probably representing reactive inflammatory changes secondary to destruction of the basement membrane zone.

As the lesion invades deeper into the cutis, except for those cases in which involution does not occur and the lesion continues its invasive and/or metastatic growth, the neoplasm soon attains its maximum size and presents the typical well-known clinical (a central, keratin-filled crateriform depression) and histologic pattern (Figs. 4A and 4B). The late stage is now reached. The epidermis at the periphery generally forms a lip over the sides of the depression, and papillomatous proliferations of keratinizing cells surrounded focally by a narrow rim of basophilic cells extend both upward into the depression and downward into the cutis. Although most of the time appearing flattened and atrophic, it is not unusual for the epidermis forming the lip of the depression to show evidence both of hyperplasia and premature keratinization. The rim of basophilic cells at the base shows variable degrees of atypicality, oftentimes extremely severe. Horn pearls and horn cysts are usually present. As a rule, the histologic pic-

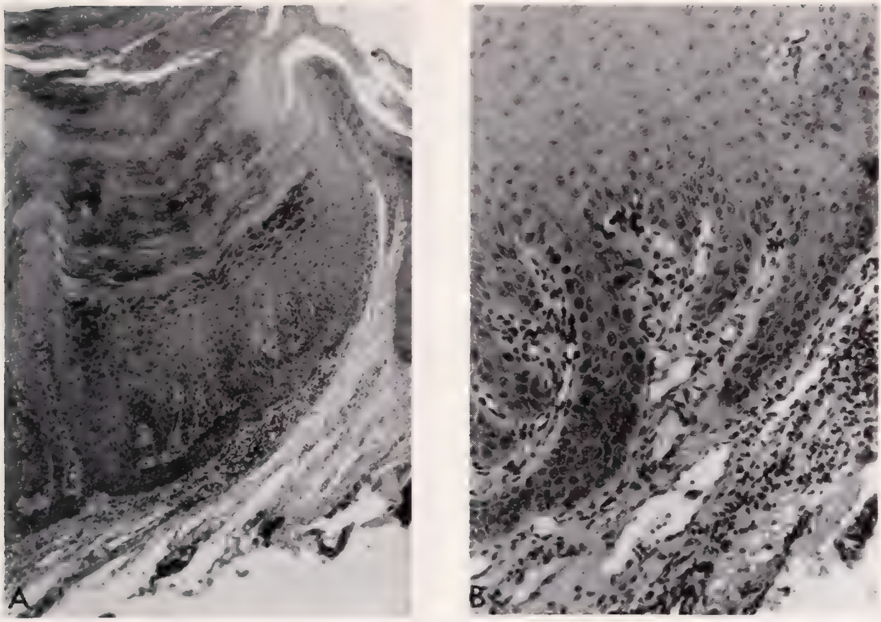

FIG. 3A. Early stage showing similar but more advanced changes plus spotty foci of parakeratosis and hyperkeratosis with absence of the granular layer and early dermal invasion by papillomatous proliferations of keratinizing cells surrounded by a rim of proliferating basophilic cells with inflammatory cell infiltrate at dermal-epidermal junction (hematoxylin-eosin × 40).

FIG. 3B. Higher magnification of base of Fig. 3A emphasizing early invasion of cutis by papillomatous proliferations of keratinizing cells with proliferating basophilic rim, vascular ectasia and inflammatory cell infiltrate at dermal-epidermal junction (hematoxylin-eosin × 100).

ture of a well-differentiated squamous cell carcinoma is now clearly evident. The surrounding stromal inflammatory cell infiltrate is more intense and exocytosis of neutrophils associated with spongiosis of the base of this tumor is frequently observed. Plasma cells, eosinophils and foreign body giant cells are only occasionally encountered. Clusters of melanophages are often noted within the subepidermal zone. Since these lesions occurred most often in sun-exposed areas, solar elastosis was a common finding. It should be emphasized at this point that both the depth of invasion and the degree of cellular atypism which one observes in the late stage may be extremely variable. In other words, both may be minimal when involution begins, thus accounting for the wide range in degrees of scarring which occurs in totally involuted cases. It is also quite conceivable, but obviously extremely difficult to prove, that a number of cases may undergo involution within either the incipient or early stages. Hence, there would be virtually no scarring.

In a relatively short period of time involution usually ensues. The early involutionary stage is characterized by dissolution of atypical cells, cessation of mitotic activity at the base of the depression with loss of the basophilic rim and progressive destruction of the papillomatous squamous cell proliferations,

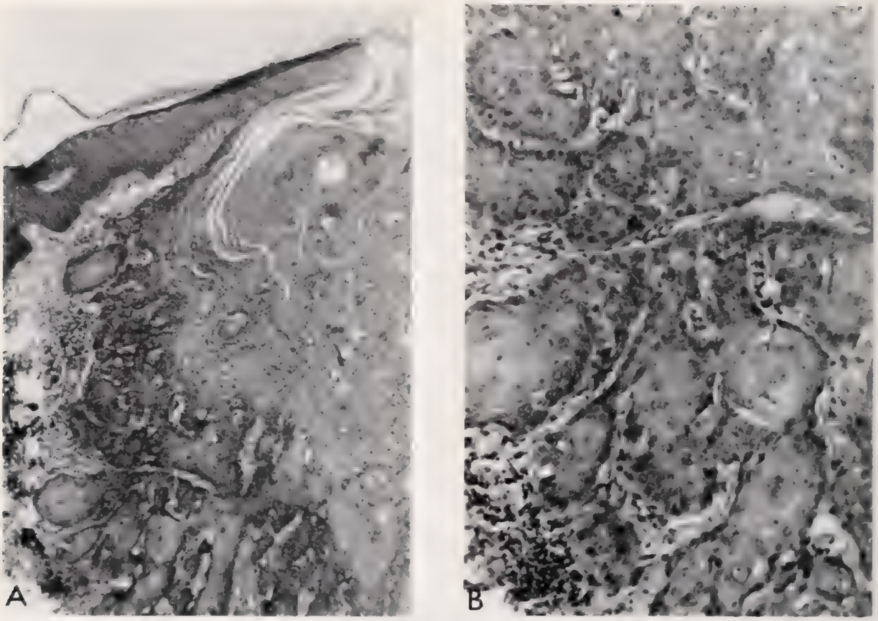

FIG. 4A. Late stage lesion showing epidermal lip, well defined crater, prominent parakeratosis and well-differentiated squamous cell carcinoma at base (hematoxylin-eosin × 40).

FIG. 4B. Higher magnification of base of Fig. 4A emphasizing well-differentiated squamous cell carcinoma with beginning horn pearl formation at left margin of photo (hematoxylin-eosin × 100).

the intraluminal ones being desquamated (Figs. 5A and 5B). The late involutionary stage is distinguished by flattening, atrophy, a return to normal maturation and upward movement of the wall of this depression with replacement of the previously invaded zone by scar tissue, producing the appearance of an open keratinous cyst (Figs. 6A and 6B). The end result is often marked by a slightly depressed scar.

Discussion

Unlike all other cutaneous malignancies, the keratocarcinoma probably can be diagnosed during its earliest clinical manifestations microscopically, even before cytologic evidence of malignancy has developed. The stimulus, whatever it may be, which initiates this lesion appears to be responsible for simultaneous increase in rate of cell production with epidermal hyperplasia and premature keratinization of epidermal cells, a combination of changes which seems to be unique in an incipient stage lesion. In approximately 50% of the incipient and early stage lesions, no pilar structures could be identified within the tumor, indicating that these lesions develop not only from pilar epithelium as is generally agreed upon (2–4), but also from epidermal keratinocytes, although origin from nondetectable intraepidermal keratinocytes could not be excluded. Even though there were no cases of the eruptive or multiple type in my series, the medical literature (2) indicates that the histopathology is identical to that of the solitary

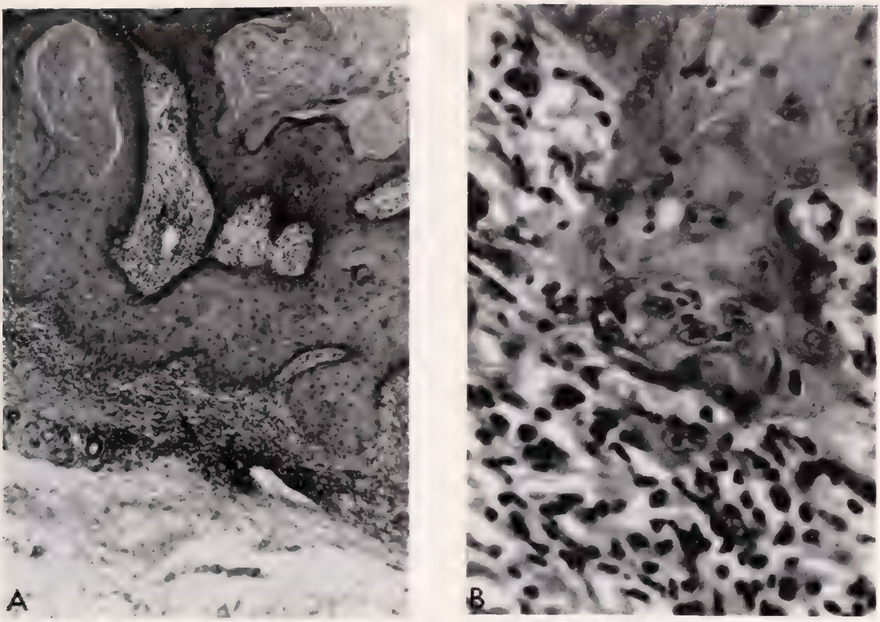

FIG. 5A. Early involutionary stage of deeply invasive lesion abutting on subcutaneous adipose tissue showing absence of atypical cells and rim of basophilic cells and dissolution of keratinized cells intermingled with conspicuous inflammatory cell infiltrate (hematoxylin-eosin, × 40).

FIG. 5B. Higher magnification of base of Fig. 5A emphasizing loss of rim of basophilic cells, dissolution of keratinized cells and intermingling of conspicuous inflammatory cell infiltrate (hematoxylin-eosin × 400).

form. Although not documented, one can hypothesize that the presence or absence of hyperkeratosis and parakeratosis as well as a hyperplastic, diminished or absent granular layer is most likely dependent upon an interplay of various factors which include rates of cell production and premature keratinization and degree of cell destruction of the proliferating basophilic rim, thus accounting for the variable histologic picture. Although a verruca vulgaris, a seborrheic keratosis and lichen planus (especially the hypertrophic form) must be considered microscopically in the differential diagnosis during this incipient stage, the absence of premature keratinization in the first two diseases and the presence of an inflammatory cell infiltrate associated with basal cell destruction in the last disease excludes them. The inverted follicular keratosis may be excluded by the conspicuous absence of squamous cell eddies. Furthermore, the early stage of a keratocarcinoma may be distinguished histologically from lichen planus and irritated lesions of the other aforementioned diseases (showing lichenoid features casually related to severe basal cell destruction) stated in the differential diagnosis of the incipient stage by the presence of a well-defined, actively proliferating basal layer in the absence of basal cell destruction. Histologic differentiation of a late stage keratocarcinoma from a squamous cell carcinoma arising from the base of an actinic keratosis may pose a difficult problem, since actinic damage is usually

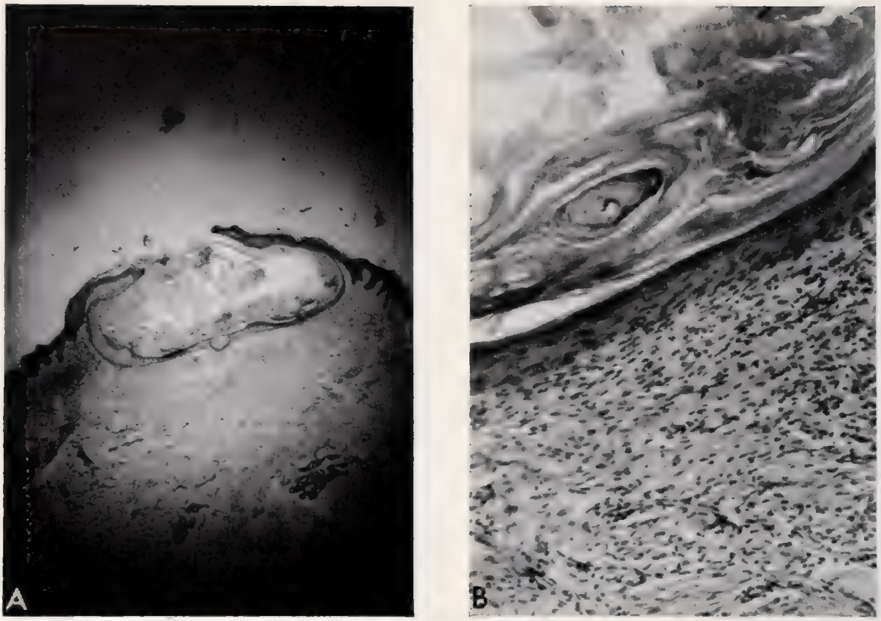

Fig. 6A. Late involutionary stage giving appearance of keratinous cyst with prominent dermal scarring (hematoxylin-eosin × 12).

Fig. 6B. Higher magnification of Fig. 6A showing small residual portion of desquamated intraluminal papillomatous squamous cell proliferation, an atrophic epidermis with normal maturation and conspicuous dermal scarring (hematoxylin-eosin × 100).

observed in the former and the latter may occasionally manifest itself with a central crateriform depression. However, the relatively long duration and slow growth of the latter usually distinguishes them. Whatever the case may be, the lesion should be thoroughly removed or destroyed. A late involutionary stage keratocarcinoma may resemble microscopically a keratinous cyst showing scarring from previous trauma. The usually greater depth of scarring along with the relatively short clinical picture in the former helps to differentiate them.

A pathologic process is a dynamic event, the clinical and histologic features depending upon the stage. This is true of virtually all disease processes. Unfortunately, most clinicians and pathologists alike are familiar with a single characteristic microscopic picture of a particular disease process. Thus, when faced with a variation of the well-known, typical histologic features, either a diagnosis cannot be made or the lesion is interpreted incorrectly. Such is the case with the keratocarcinoma. Incipient and early stage lesions are usually diagnosed as verrucae vulgares and seborrheic keratoses and late involutionary stage lesions are most often diagnosed as keratinous cysts. Although microscopic identification of the involutionary stages may be, perhaps, only of academic interest to the clinician, histologic recognition of an incipient and early stage lesion is of vital importance to the patient. Knowledge of such a lesion will permit the clinician to thoroughly eradicate it in its initial stages and, hence, prevent future disfiguring scars and or possibly destructive or fatal invasive and metastatic disease.

The keratocarcinoma is a malignant lesion and should be treated as such. Although it represents a form of squamous cell carcinoma, it is recommended that it be termed a keratocarcinoma. In this way the clinician is not only presented with a more informative histologic picture, but also realizes that he is dealing with a lesion which shows a high rate of spontaneous regression and may thereby modify his treatment accordingly.

Summary

A histologic chronology of the clinical course of the keratocarcinoma (so-called keratoacanthoma) is detailed. One-hundred fifty-nine solitary consecutive cases were carefully studied and categorized into five distinct chronological stages—incipient (6% of cases), early (43% of cases), late (45% of cases), early involutionary (3% of cases) and late involutionary (3% of cases). Simultaneous increase in rate of cell production with epidermal hyperplasia and premature keratinization of epidermal cells appear to represent the hallmarks of an incipient stage lesion. In addition to pilar epithelium, origin from epidermal keratinocytes seems likely. This is a malignant lesion and it is proposed that it be termed and treated as such. It is important to be able to diagnose this lesion in its incipient and early stages so that complete removal may be performed in order to prevent future disfiguring scars and/or possibly destructive or fatal invasive and metastatic disease.

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Preoperative Diagnosis of the Meckel's Diverticulum by Sequential 99m Technetium Pertechnetate Scanning

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ABSTRACT

The preoperative diagnosis of bleeding Meckel's diverticulum in a child was confirmed by scanning with 99m Technetium Pertechnetate. At surgery, ileal ulceration was observed adjacent to the diverticulum which revealed a small nodule of pancreatic tissue as well as parietal acid-secreting cells.

The technique of sequential scanning is described and its advantages over static scanning emphasized.

Preoperative diagnosis of Meckel's diverticulum is often difficult, whether by clinical examination or conventional methods (1–3). Radioisotope scanning as a diagnostic aid has been reported recently in several cases (4–7). This method deserves more extended application as well as further study for technical modification.

The purpose of this report is to encourage more use of radioisotope scanning in patients suspected of having Meckel's diverticulum and to emphasize in some detail the most desirable technical features of sequential scanning. We found the simultaneous visualization of the Meckel's diverticulum and the stomach during the early two-hour period of the dynamic sequential scanning very useful in confirming the diagnosis.

Case Report

A 28-month-old girl was admitted to the Mount Sinai Hospital Services of City Hospital Center at Elmhurst with a two-hour history of passing bloody stools. The blood was described as bright red and mixed with the stool. The parents had noted no evidence of abdominal pain, nausea, vomiting, or other symptoms. The family and neonatal history were noncontributory.

At eighteen months of age, the patient had been admitted to another hospital with a six-day history of port wine-colored stool and intermittent passage of bright red blood per rectum. There was no vomiting, hematemesis, or abdominal pain. Physical examination was unremarkable; stools gave a positive Guaiac test. Laboratory data included hematocrit of 22% and normal white blood cell and platelet counts, prothrombin time, and partial thromboplastin time. Radiographic studies including chest, upper gastrointestinal series, and barium enema were reported as within normal limits. Sigmoidoscopy was negative. The child received transfusions and was discharged with the diagnosis of gastrointestinal bleeding, etiology undetermined.

Physical examination on admission to our hospital, revealed a pale, normally developed infant in no distress. The blood pressure was 110 mm of Hg/60 mm of Hg; pulse rate was

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regular at 110 beats per minute; respiration 28 per minute. Physical findings were negative, except for grossly bloody stool on rectal examination. A nasogastric tube was passed which returned only clear gastric juice.

Laboratory data: hemoglobin 8.5 gm%; hematocrit 27%; white blood cell count 7,800 with a normal differential count. The reticulocytes were 1.0%, and platelets 214,000 per cubic mm. The prothrombin time was 12.8 sec. with a control of 11.7 sec. The partial thromboplastin time was 37.5 sec. and control 39.1 sec. The clot retraction was 3+ in one hour and the serum fibrinogen level was 170 mgm %. The electrolytes were within normal limits.

During the first 12 hours, the patient's vital signs remained stable and no further bloody stools were passed. After 16 hours, the hematocrit dropped to 24%. The patient was given 150 cc of packed red blood cells.

An abdominal scan with 99m Tc-Pertechnetate was performed 24 hours after admission. A round focal area of increased activity in the right mid-abdomen was visualized simultaneously with stomach activity (Fig. 1). A preoperative diagnosis of Meckel's diverticulum was made, and the patient was taken to the operating room where a Meckel's diverticulum, 60 cm from the ileocecal valve was found. The adjacent ileal mucosa was ulcerated. The diverticulum-bearing segment of ileum was resected with end-to-end anastomosis. Incidental appendectomy was also performed.

Simultaneous scanning of the surgical specimen confirmed the high concentration of the technetium in the parietal cell portion of the diverticulum (Fig. 2). The postoperative course was uneventful and the child was discharged on the 9th postoperative day.

Scanning Method

The patient was prepared by emptying of the stomach by means of a nasogastric tube and intravenous injection of 50 mgm of sodium iodide to block background activity. These procedures were done approximately one hour before the scanning. The patient was placed in the supine position under a Nuclear-Chicago pho gamma H.P. Camera with videotape unit attachment. 1.5 mCi of 99m Tc Pertechnetate (approximately 100 μCi per Kg body weight) was injected through a left leg vein. Sequential scintiphotos (Fig. 1) were taken starting immediately following the injection of the isotope. The last photo was taken 4 hours and 40 minutes after the injection. Approximately 200,000 to 400,000 counts were taken for each view, depending on the background activities.

The surgical specimen of the Meckel's Diverticulum and appendix were scanned simultaneously under the 5-inch Picker Magnascanner. This was done approximately 20 hours after the preceding day's injection for the preoperative scanning (Fig. 2).

Histology

Histologic study of the specimen revealed normal ileal mucosa lining the ileal segment and gastric glands lining the diverticulum. The latter contained numerous parietal, acid-secreting cells. At the junction of the diverticulum, grossly evident ulceration was identified. The ulcer crater was composed of necrotic debris over a granulation tissue base with surrounding fibrosis. The muscularis propria was intact (Fig. 3). The intramural nodule at the apex of the diverticulum was identified as pancreatic parenchyma. The vermiform appendix revealed no gross or microscopic abnormality.

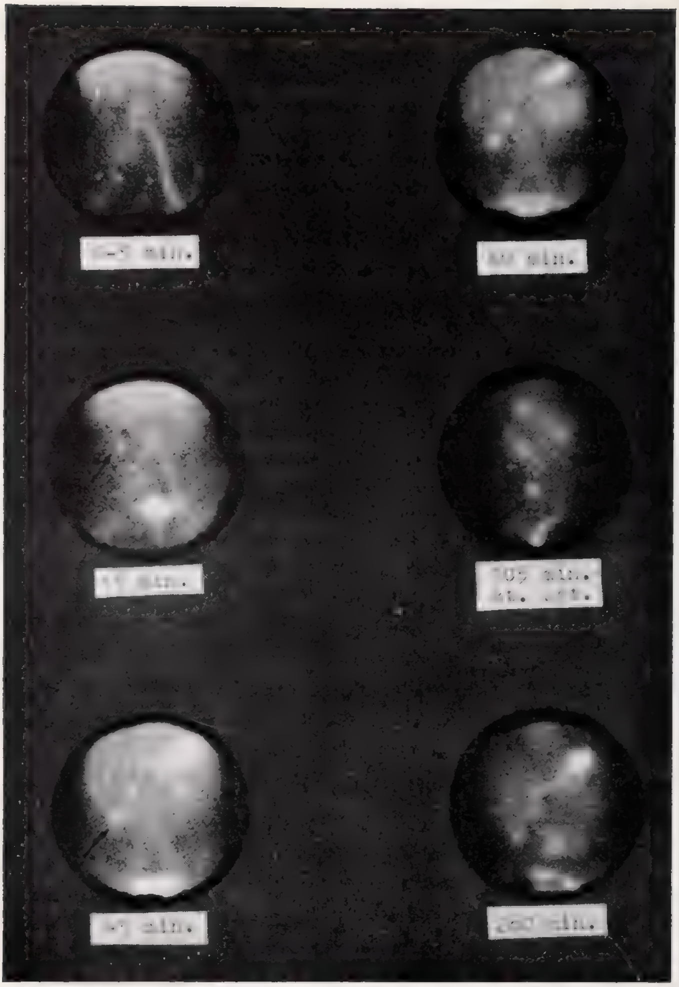

Fig. 1. Sequential Scans of the Abdomen. The time after injection of 99m Tc Pertechnetate is labeled for each view. All scans, except the one at 105 minutes, are anterior views. The white cross marks represent the costal margins (upper), umbilicus (single mark in the middle), and pubic ridge (lower). Notice the intravascular and hepatic activity in the early phase, and later simultaneous visualization of the Meckel's diverticulum (arrow), stomach and duodenal bulb.

Discussion

Although clinical manifestations of Meckel's diverticulum are most common in the pediatric age group, and over 60% of the cases are reported in children under the age of 10 (1, 8), the average mortality related to the lesion in several surgical series is 6%, with a large proportion of the deaths occurring in the elderly.

Most symptomatic Meckel's diverticula contain gastric mucosa which is responsible for the ulceration of the adjacent ileal mucosa and subsequent complications, such as bleeding, obstruction, and inflammatory changes.

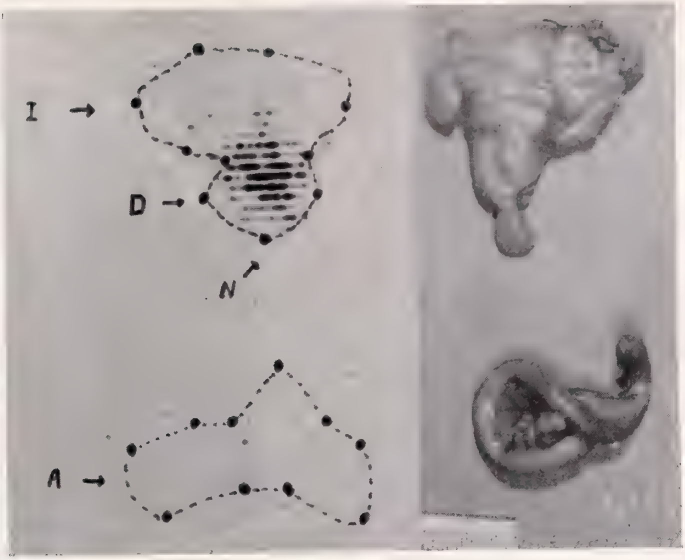

Fig. 2. Scan of the Surgical Specimen. Notice the high activity in the diverticulum (D), while the ileal segment (I), the intramural nodule of pancreatic tissue (N) at the tip of the diverticulum and appendix (A) show no activity.

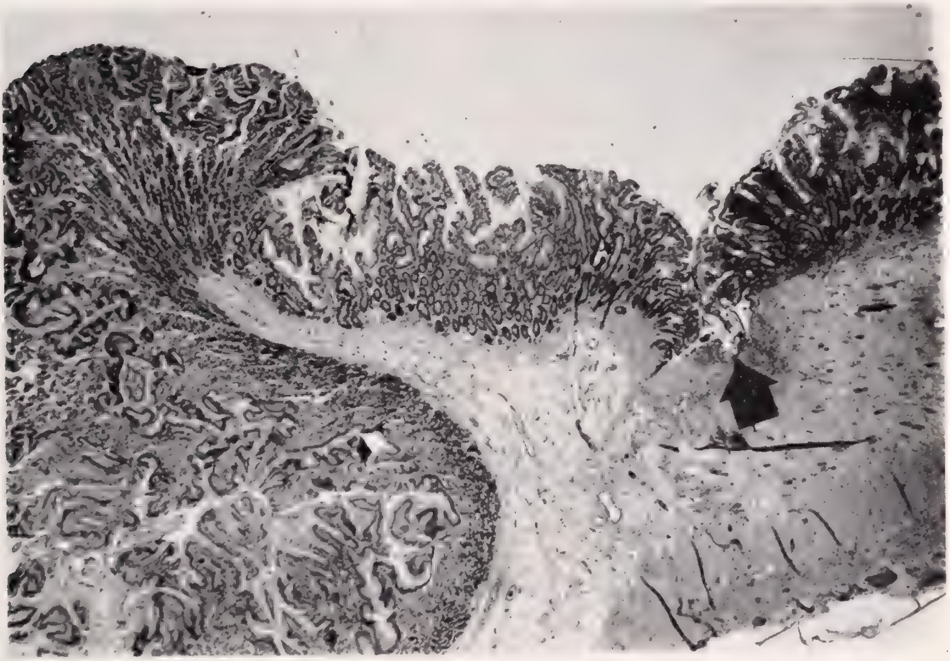

Fig. 3. Photomicrograph showing ulcerated mucosa (arrow) at the junction of ileal mucosa (right) and gastric-lined diverticulum (left) (H and E × 25).

99m Tc Pertechnetate in vivo concentrates in the stomach, thyroid, salivary glands, urinary bladder, and colon (9). Ectopic gastric mucosal tissue (parietal cells) in Meckel's diverticulum takes up high concentration of pertechnetate (4–7). Berquist et al (6) showed, by counting their surgical specimen, 6- to 9-fold concentration of the activity in the gastric mucosa of the diverticulum compared to the adjacent ileal mucosa. This unique correlation of histologic components and clinical symptomatology should enable technetium scanning to be of great use as a diagnostic method in symptomatic cases. However, one should be careful in making diagnosis by this method, as false-positive scans (10) and false-negative scans (7) were mentioned in the literature.

We believe that gamma-camera scanning is preferable to rectilinear scanning, because the diverticulum may be located at a variable distance from the collimator and thus may be out of the focal range of the latter apparatus.

Our scans were done in sequence, both through the A-Scope of the camera at the time of actual procedure and later by playback of the videotape recorder to the B-Scope. The latter enables more controlled serial scans to be made. The Meckel's diverticulum and the stomach were simultaneously visualized as early as 5–10 minutes after the injection of the isotope. Except for the activities in the stomach, duodenal bulb, bladder, and aorta (early stage), no other activity was noted to obscure the localization of the diverticulum during the early 2 hour period. After 3 hours, increased intestinal activity was noted. This may be confusing if delayed scanning alone is done.

It would appear that scanning within the period of 30 minutes to 2 hours after the injection is indicated. If available, dynamic recording in the initial 2 hours, as done in the present case, would be useful. In this case, simultaneous visualization of the Meckel's diverticulum and stomach activity was easily accomplished with the videotape recording.

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Clinical Studies with Cefazolin : A New Cephalosporin Antibiotic

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Abstract

The clinical efficacy of cefazolin, a new cephalosporin antibiotic, was evaluated in 39 hospitalized patients with serious infections. Bacteremia was present in 14 of the patients. Pathogenic bacteria were isolated from 33 patients; the MIC of cefazolin was greater than 12.5 μg/ml in 7 of the bacterial isolates. Serum and urine concentrations 2 hours after administration of cefazolin did not differ significantly for the intramuscular or intravenous routes. Thirty-six of the patients were considered cured of their infection. One patient developed rash and 4 other patients eosinophilia while on cefazolin therapy.

Introduction

Cefazolin, 7-[1-(1H)-tetrazolylacetamidol]-3-[2-(5-methyl-3,3,4-thiadizolyl)-thiomethyl]-Δ^3-cephen-4-carboxylic acid, is a new semisynthetic cephalosporin antibiotic possessing a broad spectrum of antimicrobial activity including most strains of penicillin sensitive and penicillin resistant Staphylococcus aureus, Diplococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, indole-negative Proteus and Klebsiella sp. (1–4). Cefazolin is well tolerated intramuscularly and intravenously and the blood levels attained are higher and more sustained than other cephalosporins (5). It appears to be less nephrotoxic than cephaloridine (6) and demonstrates less immunologic cross-reactivity with penicillin than either cephalothin or cephaloridine (7). One investigation reported less phlebitis following intravenous administration of cefazolin than with cephalothin (8).

The present study was undertaken to evaluate the clinical efficacy, and safety of cefazolin in the treatment of seriously ill hospitalized patients with infection.

Materials and Methods

Thirty-nine patients hospitalized at The Mount Sinai Medical Center with serious infections from December 1972 through March 1974 were included in the study. Cefazolin was administered parenterally in doses ranging from 1.5 to 6.0 grams/day, given in divided doses. In thirty-six of the patients cefazolin was the only antimicrobial agent administered.

A completed blood count (CBC), urinalysis, blood urea nitrogen (BUN), and serum creatinine, glucose, electrolytes, calcium, phosphorus, bilirubin, alkaline phosphatase, glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic

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transaminase (SGPT) were determined in each patient before, during and after therapy with cefazolin.

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of cefazolin for the infecting organisms were determined by a standard two-fold tube dilution method. The inoculum consisted of a 10^{-3} dilution of an overnight growth of the microorganism. The MIC was defined as the lowest concentration of antibiotic in which no visible turbidity was observed after incubation for 18 hours at 37°C. The MBC was defined as the lowest concentration of antibiotic without visible growth after an 18 hour incubation at 37°C following wire-loop subcultures onto agar plates. During the course of therapy, blood, urine, and when appropriate, cerebrospinal (CSF), synovial, and ascitic fluid concentrations of cefazolin were assayed by the pennicylinder agar method (9).

All patients were evaluated for clinical and bacteriologic response. Patients were considered cured of infection if clinical symptoms and signs abated, the infected site was sterilized, and there was no recurrence of infection after discontinuing therapy.

Results

Thirty-nine patients, 13 males and 26 females, ranging in age from 21 to 90 years, were admitted to the study (Table I). Bacterial infection was proved in 29 patients and strongly suspected in 10 others. Seven additional patients did not have bacterial infection, but were included in the pharmacologic studies.

There were 14 patients with bacteremic infections. Five were caused by Staphylococcus aureus, three of which were secondary to indwelling intravenous catheters; one followed delivery, and no obvious source was found for the other. Diplococcus pneumoniae bacteremia was associated with lobar pneumonia in one patient; the other patient was a drug addict with no obvious source of infection. Two isolates from blood cultures of Escherichia coli, two of Klebsiella sp., and one Proteus mirabilis were associated with urinary tract infections. Two bacteremias secondary to E. coli were associated with vertebral osteomyelitis, and Neisseria flava was isolated from a patient with subacute bacterial endocarditis.

Cefazolin was evaluated in seven patients with pneumonia (Table I). Diplococcus pneumoniae was cultured from transtracheal aspirates in two, Enterobacter aerogenes from pleural effusion in one, Klebsiella sp. from multiple sputum cultures in three, and Staphylococcus aureus from sputum in another patient.

Two urinary tract infections were caused by Escherichia coli and one by P. mirabilis.

There was one patient with staphylococcal arthritis and 6 patients with soft tissue infections, five of which were secondary to Staphylococcus aureus and one secondary to Streptococcus pyogenes.

In six patients bacterial isolations were not considered to be diagnostic. This

TABLE I

Clinical Data of Patients Treated with Cefazolin

Pt. No.	Age/Sex	Clinical Diagnosis	Bacterial Isolate	Site of Culture	Clinical Response
1	34/M	Drug addict sepsis	D. pneumoniae	Blood	Cure
2	22/F	Elective caesarean section; sepsis	Staph. aureus	Blood, lochia	Cure
3	52/F	Thrombotic thrombcytopenic purpura; postsplenectomy; on steroids; sepsis	Klebsiella	Blood, urine, cup catheter	Cure
4	63/F	Diabetes; atherosclerotic heart disease; sepsis	Staph. aureus	Blood, IV site	Cure
5	21/F	Acute pyelonephritis	E. coli	Blood	Cure
6	58/F	Stage 4-B Hodgkins disease; steroids; right renal stone; urosepsis	Proteus mirabilis	Blood, urine	Cure with antibiotics and right pyelolithotomy
7	68/M	Vertebral osteomyelitis; sepsis	E. coli	Blood	Cure
8	30/F	Drug addict; pneumonia	D. pneumoniae	Blood	Cure
9	24/F	Anorexia nervosa; hyperalimentation; sepsis	Staph. aureus	Blood; hyperalimentation catheter	Initial response to therapy followed by meningitis that responded to oxacillin
10	43/F	Connective tissue disease; sepsis	Staph. aureus	Blood	Initial response but relapsed after 4 weeks of therapy and responded to clindamycin
11	36/F	Small bowel infarction on oral contraceptives; hyperalimentation; urosepsis	Klebsiella sp.	Blood, urine	No response—responded to gentamicin
12	85/F	Urinary tract infection	E. coli	Blood, urine	Cure
13	38/F	Biliary cirrhosis; endocarditis; osteomyelitis of wrist	Neisseria flava	Blood	Cure on Cefazolin and gentamicin
14	56/F	Postcraniotomy for meningioma; sepsis	Staph. aureus	Blood, IV catheter	Cure
15	79/F	Diabetes mellitus; hypertension; pneumonia	D. pneumoniae	Transtracheal aspirate	Cure
16	30/F	Drug addict; pneumonia	D. pneumoniae	Blood	Cure
17	60/F	Postcraniotomy for posterior communicating artery aneurysm; pneumonia	D. pneumoniae	Transtracheal aspirate	Cure
18	54/M	Diabetes mellitus; pneumonia	Klebsiella sp.	Sputum	Cure
19	43/M	Pneumonia	Klebsiella sp.	Sputum	Cure, 5% eosinophilia
20	69/M	Chronic lung disease; lung abcess; on carbenicillin for pseudomonas bronchitis	Klebsiella sp.	Sputum	Cure
21	58/M	Chronic lung disease; alcoholic; bilateral empyema	Enterobacter aerogenes	Pleural fluid, urine	No response—bacteria resistant to cefazolin
22	25/F	Down's syndrome; congenital heart disease; pneumonia	D. pneumoniae	Throat	Cure
23	53/M	Pneumonia	Staph. aureus	Sputum	Developed rash on cefazolin—changed to clindamycin
24	55/F	Asthma; pneumonia		—	Cure, 8% eosinophilia
25	23/M	Nelson's syndrome; aspiration pneumonia following transsphenoidal hypophysectomy	—	—	Cure
26	90/M	Chronic lung disease; bronchopneumonia	—		Cure
27	72/M	Cerebrovascular disease; bronchopneumonia	E. coli, Enterobacter aerogenes	Sputum	Cure

TABLE I—*continued*

Pt. No.	Age/Sex	Clinical Diagnosis	Bacterial Isolate	Site of Culture	Clinical Response
28	23/F	Grave's disease; bronchopneumonia	—	—	Cure, 6% eosinophilia
29	66/F	Diabetes mellitus; hypertension; urinary tract infection	E. coli	Urine	Cure
30	73/F	Atherosclerotic heart disease; pericarditis, urinary tract infection	Proteus mirabilis	Urine	Cure
31	56/F	Left ulnar nerve transplant with wound infection	Staph. aureus	Elbow wound	Cure
32	24/F	Regional enteritis; on steroids; buttock abscess	Staph. aureus	Buttock abscess	Cure
33	58/M	Alcoholic cirrhosis; diabetes mellitus; groin abscess	Staph. aureus	Groin	Cure
34	65/F	Chronic lymphocytic leukemia; cellulitis of right leg	Strep. pyogenes	Subcutaneous aspirate of cellulitis	Cure
35	59/F	Erysipelas		—	Cure
36	69/M	Resection of sacral chordoma; postop wound infection	Staph. aureus, Proteus mirabilis	Wound	Improved
37	76/M	Infected pacemaker site	Staph. aureus	Pacemaker site	Improved on cefazolin alternating with cephalothin
38	64/F	Sjogren's syndrome; steroids; septic arthritis of left knee	Staph. aureus	Knee aspirate	Effusion sterilized on cefazolin—changed to oxacillin after 14 days due to continued effusion
39	53/F	Discoid lupus erythematosus; infected right shoulder	—		Cure

group consisted of four cases of pneumonia and one each of erysipelas and septic arthritis. All had clinical signs and symptoms of bacterial infection and all responded promptly to the administration of cefazolin. They were included as infected cases suitable for analysis.

There were three therapeutic failures. Patient 9 (Table I), a 24-year-old woman with anorexia nervosa developed staphylococcal septicemia from an infected hyperalimentation line. Initially she responded to 500 mg of cefazolin IV every six hours; on the eighth day of therapy she developed lethargy, nuchal rigidity and cerebrospinal pleocytosis with 45 white blood cells, 97% of which were polymorphonuclear neutrophils. Though gram-stain and culture of the cerebrospinal fluid were negative, a countercurrent immunoelectrophoresis assay of cerebrospinal fluid for staphylococcal cell-wall products was positive. Therapy was changed to oxacillin and rapid improvement ensued. The cefazolin level in the serum at two hours after a dose was 31.9 μg/ml while the cerebrospinal level was <2.5 μg/ml CSF. Patient 10, a 43-year-old woman with a collagen vascular disease and staphylococcal bacteremia was treated for four weeks with 4 grams of parenteral cefazolin per day. Blood cultures remained positive after four weeks of cefazolin therapy and parenteral clindamycin was begun. After eight days of clindamycin the left olecranon bursa became hot and tender and an aspirate grew S. aureus. Six weeks of clindamycin therapy led to resolution of this problem.

The third treatment failure was a 36-year-old woman (Patient 11) who developed septicemia secondary to Klebsiella sp. following surgery for small bowel infarction. After eight days of therapy with 4 grams/day of intramuscular cefazolin, no clinical or bacteriologic improvement was noted. The serum level, 2 hours after a dose, was 56.5 μg/ml; the MIC and MBC of the organism were 3.1 μg ml and 6.25 μg ml respectively. The patient subsequently responded to gentamicin.

The effect of cefazolin therapy in four patients could not be evaluated. Patient 13 with N. flava endocarditis, and patient 37 with staphylococcal soft tissue infection associated with a cardiac pacemaker both received additional effective antimicrobial agents. Patient 23 with stephylococcal pneumonia without bacteremia developed a generalized maculopapular rash on the fifth day of therapy which resolved when cefazolin was discontinued. Patient 38 with staphylococcal arthritis was treated with cefazolin; improvement followed and although joint aspirates were sterile, therapy was inexplicably changed to oxacillin.

Besides the patient who developed a drug rash, five patients developed eosinophilia. Three had modest elevations of serum alkaline phosphatase and glutamic-oxaloacetic transaminase, but discontinuance of cefazolin was not required. Phlebitis was not a complication in any of the 24 patients treated intravenously. Two of 30 patients who received intramuscular cefazolin complained of pain and refused further parenteral therapy with any medication.

The MICs and MBCs of cefazolin for the 33 isolates from the patients in this study are presented in Table II. D. pneumoniae was highly sensitive, with all four strains sensitive to ≤0.15 μg/ml. All 12 isolates of Staphylococcus aureus were inhibited by ≤1.55 g/ml. The gram-negative isolates were somewhat less sensitive. All five strains of E. coli and 3 of 4 Klebsiella sp. isolates were sensitive to ≤3.13 μg/ml; one strain of Klebsiella sp. was resistant to 50 μg/ml of cefazolin.

Serum and urinary concentrations of cefazolin obtained two hours following administration are presented in Table III. Following one gram of cefazolin administered every six hours, the serum levels ranged from 10.9 to 100 μg/ml and the urine levels from 0.34 to 8.55 mg/ml. The serum and urine levels found two hours after IV and IM administration were not significantly different. Penetration into synovial and ascitic fluids was measured in one instance each and was found to be 17 and 67% of the simultaneous serum levels, respectively. Penetration into the CSF was minimal in the one instance measured (vide supra). The overall response rate to cefazolin was 92% (36 of 39 patients).

Discussion

Overall, cefazolin was found to be an effective antimicrobial agent for the treatment of patients with infections due to sensitive bacteria. The development of meningitis due to a sensitive microorganism while on therapy with a cephalosporin derivative has been well documented (9) and is probably due to the poor penetration of this class of antibiotics into the cerebrospinal fluid. Ishiama et al (10) found only 0.4 μg/ml of cefazolin in the cerebrospinal fluid after an intravenous dose of 10 mg/kg in four healthy volunteers. Similarly,

TABLE II

Sensitivities of Clinical Isolates to Cefazolin

Cefazolin (μg/ml)	Pen-S* *Staph. aureus*		Pen-R† *Staph. aureus*		*S. epidermidis* & *Micrococcus* sp.		*Strep. pyogense*		*Diplococcus pneumoniae*		*E. coli*		*Klebsiella*		*P. mirabilis*		*N. flava*		*Enterobacter*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
.055									1											
.01																				
.02									1											
.04			3		1				1	1										
.075			2	1		1	1	1		2										
.15									1											
.36	2			3									2							
.75	1	1																		
1.55		2	4	1	2					1	2	1	1	1						
3.13											3			1						
6.25				1		1						2		1	1		1	1		
12.5				1		1						1								
25.				1								1	1		1					
50.				1										1						
> 50.																2			1	1

* Pen-S, sensitive to penicillin G.

† Pen-R, resistant to penicillin G.

TABLE III

Serum and Urine Concentrations of Cefazolin

(μg/ml)

Dose 2 g q 8 hr	1.0 g q 6 hr		1.0 g q 8 hr	0.5 g q 6 hr		0.5 g q 8 hr
Route IM	IV	IM	IM	IV	IM	IM
122/1085*	18/338	44/3180	24/26000	32/2480	7.9/1305	176/3000
	11/8550	47/4770	167/—			
	60/—	57/3480				
	21/—	28/3480				
	68/1200	140/3750				
	53/—	21/—				
	—/690					
	62/2060					
	100/—					
	82/540					
	47/840					
	64/1010					
	50/—					
	58/7800					
Average	53/2560	56/3730				

* Serum/urine.

Reller et al (3) found 0.5 μg/ml in the CSF after 1 gm cefazolin was administered IM in five patients with noninflamed meninges. Additionally, only 1.0 μg/ml of cefazolin activity was found in cerebrospinal fluid when the serum level was 21.9 μg/ml. In the other therapeutic failure the organism isolated was susceptible in vitro and the serum levels observed were far in excess of the MICs for the organism. Quinn et al (11) reported a therapeutic failure in a case of acute staphylococcal endocarditis in which reexamination of the infecting organism showed a large inoculum effect; this is not unusual with staphylococci.

In vitro studies may not always correlate with clinical responsiveness. One patient with necrotizing pneumonia secondary to Klebsiella, for which the MIC of cefazolin was 25 μg/ml, responded favorably and was cured.

Serum and urine levels of cefazolin varied considerably in our patients. The drug was administered by the ward nurses and samples were often obtained by the house staff, so that duration of infusions and sampling time varied greatly. These results are similar to other published data (2). In this study we noted that the levels produced by the intramuscular route did not differ significantly from the intravenous route. Penetration into joint and ascitic fluid was considered adequate in the one case studied.

Nephrotoxicity was not observed in any of the patients treated. In all studies to date with cefazolin, nephrotoxicity has not been reported (2, 3, 11–14).

It can be concluded from our studies that cefazolin is a safe antibiotic, effective against a wide variety of gram-positive and gram-negative bacteria. Thus intramuscular cephalosporin appears to be an alternative to cephaloridine, and does not appear to have any clinical nephrotoxity associated with cephaloridine.

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The Respiratory Distress Syndrome and Glucocorticoid Treatment: The Case for Enzyme Induction

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Introduction

The concept of induction in biological systems is a protean one. Embryologists, led by Spemman, utilized the term "induction" to describe the influence of tissue grafts such as optic cups (1) or dorsal blastopore lip (2) on presumptive or undifferentiated tissues in developing organ systems. Biochemists have used the term to characterize the action of a chemical substance on a system which causes increased de novo synthesis of a protein substance, either structural or enzymatic. The induction of enzymes which catalyze catabolic reactions and the activity of which increases in the presence of the catabolized substrate such as E. coli B-galactosidase in the presence of lactose (3), and the effect of phenobarbital on liver microsomal enzymes such as bilirubin glucuronyl transferase (4–6), represent prime examples of this phenomenon.

The most recent usage of the induction concept has been its application to describe hormonal mediation of enzymatic and structural protein synthesis in mammalian systems. The effects of estrogen as an inducer of structural protein synthesis (7–9), and corticosteroids on the synthesis of many enzyme systems (10-15) have excited great interest since they represent an advance in our understanding of the control mechanisms of mammalian gene expression. But the most intriguing and perhaps indistinct usage of the term induction has been in the field of perinatology where claims of induction of maturity in the respiratory system of premature infants vulnerable to Respiratory Distress Syndrome (RDS) have recently been made (16–19). This usage of induction is fascinating because it represents a major attempt by man to affect the complex control systems which regulate gene expression and cellular differentiation in the developing fetus. Whether these efforts to modify developmental progress represent induction as the biochemist or embryologist understands it, and what the actual effect achieved is, deserve attention. The putative induction of lung maturity in fetuses requires clarification according to accepted biochemical definitions.

Hormonal Model

The major criterion that must be fulfilled to demonstrate induction in a biochemical sense is de novo synthesis of protein. A means of ruling out activation or derepression of enzyme activity must be used. Obviously, addition and deletion of the "acting agent" and observation of a resultant increase and decrease of activity would not be sufficient to demonstrate true induction. Actinomycin-D and cyclohexamide (acti-dione), agents which interfere with transcription and translation respectively, were used to identify induction. If these agents inter-

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fered with the associated increase in activity of an enzyme or increase in a structural protein when an inducer was introduced, the system was judged to be an inducible one. With the advent of immunochemical assays, the actual quantity of a protein can be assayed as an increase in precipitable radioactive counts. Other biophysical parameters such as sucrose density centrifugation and electrophoretic mobility assist in identifying and quantifying proteins.

The first demonstration of an inducible enzyme in mammals (1951) was the observed increase in activity of tryptophan oxygenase (L-tryptophan: oxygen oxidoreductase E.C.1.131.12) after administration of glucocorticoids (15). In the next twenty years, ovalbumin (8) and avidin (22) were shown to be induced by estrogen, and many animal enzymes were shown to be inducible with glucocorticoids, among them tyrosine aminotransferase (TAT) in rat liver (20) and hepatoma culture (21), glutamine synthetase in chick retina (12), phenylethanolamine N-methyltransferase (PNMT) in rat adrenal medulla (13), and invertase activity in the newborn rat (10).

Estrogen

The observation that a marked differentiation of hen oviduct took place under the influence of estrogen made this affected organ system a natural one to study (22). Also, with ovalbumin constituting 60–70% of the protein synthesized by the highly specialized cells of the oviduct, this system, with its almost homogeneous mRNA, provided an ideal opportunity to investigate the molecular mechanisms of induction. A series of experiments using natural estrogens or diethylstilbesterol in vivo and in cell-free systems (cfs) demonstrated that the synthesis of albumin and avidin was inducible (9, 22, 23). These experiments have taught a number of valuable lessons. Induction represents a mechanism which can control cytodifferentiation, that is, cause the appearance of a structural protein at a particular time in the developmental sequence. Furthermore, the natural process of induction can be imitated with exogenous pharmacologic doses of estrogen. The latency in the estrogen system is 3–5 days and the underlying molecular mechanism appears to act at a transcriptional level.

Glucocorticoids

The glucocorticoid induced enzymes differed from the estrogen induced enzyme systems in two respects. Firstly, all of the glucocorticoid-induced proteins which have been studied are enzymatic in nature and are thus susceptible to assays of activity (assays which may be misleading since increased activity may be interpreted to mean induction when it may not be). The second difference is that none of the enzymes investigated represented more than a very minor fraction of the cells' total protein production. Thus the elucidation of molecular mechanisms had to await the development of cell free systems and the discovery of the eukaryotic poly-adenylate rich mRNA, which escapes nuclear degradation and supposedly represents "true messenger" and which allowed bulk purification of messenger by preferential binding to nitrocellulose (24, 25).

The study of tryptophan oxygenase illustrates the historical pattern of re-

TABLE I

Glucocorticoid Induction of Mammalian Enzymes

Enzyme	Tissue	Latency	Activity Increase	Ref.
Tryptophan oxygenase	Adult rat liver in vivo	3 hrs.	15×	(29)
Tyrosine amino-transferase	Adult rat liver in vivo	2–8 hrs.	5×	(77)
TAT	Fetal rat liver culture	6–12 hrs.	4–8×	(78)
TAT	Rat hepatoma culture	15–20 hrs.	10–18×	(79)
PNMT	Rat adrenal treated in utero	1–8 days	3×	(13)
Glutamine synthetase	retina cult. from 12 day rats	48 hrs.	6×	(12)
	14 day embryos treated in utero	48 hrs.	15×	
Methionine adenosyl-transferase	rat liver in vivo	24 hrs.	1.8×	(72)

search which has enveloped most of the inducible systems. After Knox and Mehler demonstrated increased enzyme activity with steroid treatment (15), Feigelson and Greengard showed that the increased activity was a result of increased quantities of enzyme being present (26). It was proposed that the induction effect was on a transcriptional level after demonstration that induction was inhibited by actinomycin (27). In recent years, an increase in the incorporation of RNA precursors has been shown to precede the increased enzyme activity, and has reinforced the hypothesis that the site of control is at a transcriptional level (28). In order to study the precise location of this control, Shutz, Beato, and Feigelson utilized a heterologous cell free system and the polyadenylate rich mRNA fraction of liver from hydrocortisone treated rats to direct tryptophan oxygenase synthesis (29). With monovalent immunoprecipitation and other biophysical assays, they demonstrated that the specific increase in mRNA did correlate with an increased production of the enzyme, and thus confirmed the results of the Actinomycin experiments.

The conclusions that may be drawn from 20 years of experimentation with mammalian induction systems are the following: induction with glucocorticoids has a latency between 3 and 48 hours in vivo experiments (latency is to a great degree a reflection of assay sensitivity) and results in a 5- to 20-fold increase in activity (Table I). Some of the enzymes can be induced prenatally with glucorticoids (PNMT and glutamine synthetase), while others can't (TAT). In those enzyme systems that have been examined, the molecular mechanism seems to involve an increased transcription of DNA to mRNA which is subsequently translated as an increase in protein synthesized.

The Lung and Surfactant

The reader is recommended to several excellent reviews (30, 31) and texts (32) concerning the fetal, neonatal, and mature lung and surfactant. A complete review of the physiology and biosynthesis of surfactant in the lung cannot be offered here.

The portrait of the lung as a composite of spherical alveoli stabilized during expiration (reduction of radius) by a surface tension reducing phospholipid is widely accepted. The contention that the density of the lung (0.16) and the work involved in expanding and contracting 70m² of spherical surfaces, makes the spherical model untenable (30, 31, 33) has been ignored by most workers. These considerations are obviously paramount in the study of the effect of putative surfactant induction on respiratory maturity and RDS. If the spherical model is chimerical, then the currently held hypothesis of surfactant function must be discarded, and the surface tension-reducing properties of surfactant must be relegated to some other or more minor physiologic role in pulmonary function.

The presence in the lung of a substance that can reduce the surface tension of water to near 0 is incontrovertible as is the evidence that the main component of the surfactant is lecithin. The role of the surfactant, however, both in the physiology of the lung and in the pathophysiology of RDS is not as clear, although most workers have accepted its deficiency as the primary etiologic factor in the syndrome.

Although there are marked differences known between the respiratory systems in animals and man, the similarities have been cited to support the use of steroids in man. A review of the surfactant synthesis in mammals other than man is necessary for a cogent understanding of the subject.

The most detailed work on surfactant synthesis in mammals was conducted by Gluck's group with rabbits (34). Their findings indicate that there are four main pathways of phospholipid synthesis in the lung and two of these lead to lecithin synthesis (Fig. 1). As gestation proceeds, lecithin becomes an increasingly greater fraction of lung phospholipids which include sphingomyelin, phosphatidyl inositol, methylated intermediates such as phosphatidyl monomethylethanolamine and phosphatidyl dimethylethanolamine (PDME), phosphatidyl ethanolamine, phosphatidyl serine, and lecithin, approaching 50% of the total at term. Although the CDP-choline pathway, which can be identified in labeled

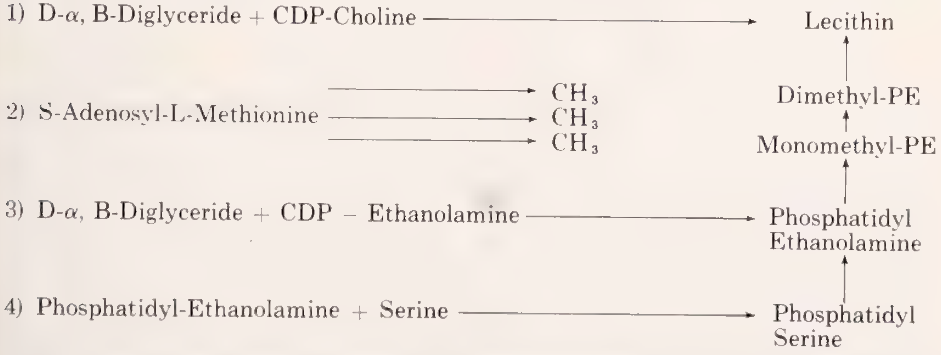
1) D-α, B-Diglyceride + CDP-Choline
Lecithin
2) S-Adenosyl-L-Methionine
CH₃
CH₃
CH₃
Dimethyl-PE
Monomethyl-PE
3) D-α, B-Diglyceride + CDP – Ethanolamine
Phosphatidyl Ethanolamine
4) Phosphatidyl-Ethanolamine + Serine
Phosphatidyl Serine

FIG. 1. Lecithin synthesis pathways. PE-Phosphatidylethanolamine; CDP-Cytidine Diphosphate. From Gluck (35).

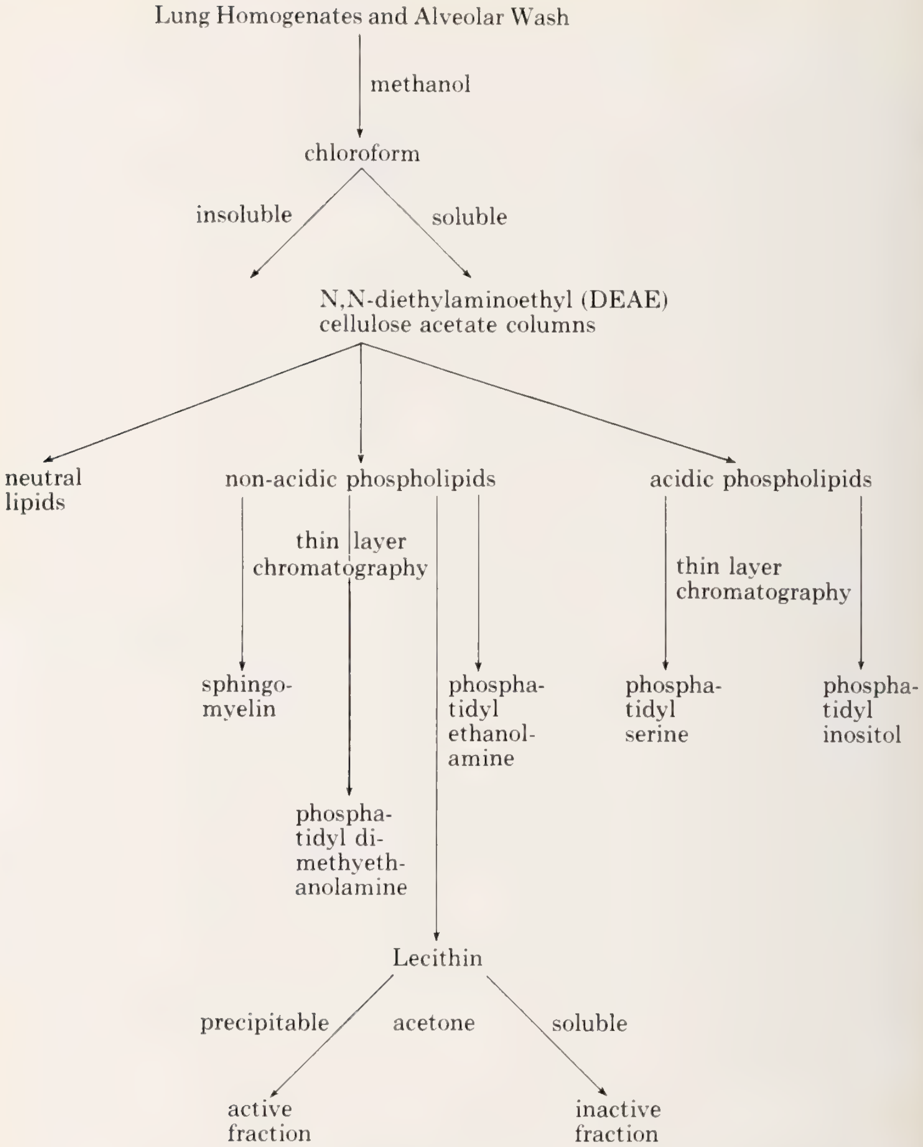
Lung Homogenates and Alveolar Wash
methanol
chloroform
insoluble
soluble
N,N-diethylaminoethyl (DEAE) cellulose acetate columns
neutral lipids
non-acidic phospholipids
acidic phospholipids
thin layer chromatography
thin layer chromatography
sphingomyelin
phosphatidyl ethanolamine
phosphatidyl serine
phosphatidyl inositol
phosphatidyl dimethyethanolamine
Lecithin
precipitable
acetone
soluble
active fraction
inactive fraction

FIG. 2. Separation and isolation of lecithin. From Gluck et al (35).

incorporation studies, declines steadily throughout gestation, it appears to represent the major pathway by which surfactant is synthesized (90%). The CDP-ethanolamine pathway, on the other hand, is the most active in vitro phospholipid pathway throughout gestation and peaks 5 days prior to term. Yet it does not contribute significantly to the production of lecithin since its production of lecithin depends on the methylation pathway which peaks 3 days prior to term and only represents 10% of the total lecithin production at term (31 days).

A major factor in the control of surfactant concentration in the fetal rabbit is timed release at 29 days of lecithin, supposedly from intracellular microsomal stores which are acetone soluble and presumably inactive, to the alveolar surface where it is acetone precipitable and active (35) (Fig. 2). The significance of acetone soluble and precipitable fractions is in question. This release phenomenon occurs concurrently with the earliest viable day for premature delivery when the neonate will not develop RDS.

The possibility that the 10% of the lecithin contributed via the CDP-ethanolamine pathway (peaks day 26–27) in cooperation with the methylation path (peaks one day later) results in a small but important pool of lecithin which is released at day 29 is intriguing (Fig. 3). This surfactant pool provides a teleologic explanation of the timed sequence of peak enzyme activities which culminate at day 29 with a viable fetus even though the CDP-choline path has declined steadily throughout. Thus, the sharp rise in acetone-precipitable lecithin which is observed on day 29 and presages viability may be initiated, not by a change in intracellular binding necessarily, but by the production of a new pool of lecithin derived from CDP-ethanolamine and methylation pathways.

The onset of breathing in a neonate born after the 29th gestational day appears to initiate a massive release of intracellular lecithin to the acetone-precipitable pool causing a 20- to 30-fold increase in concentration. Since 90% of the alveolar wash lecithin at this time is labeled with choline, this fraction probably

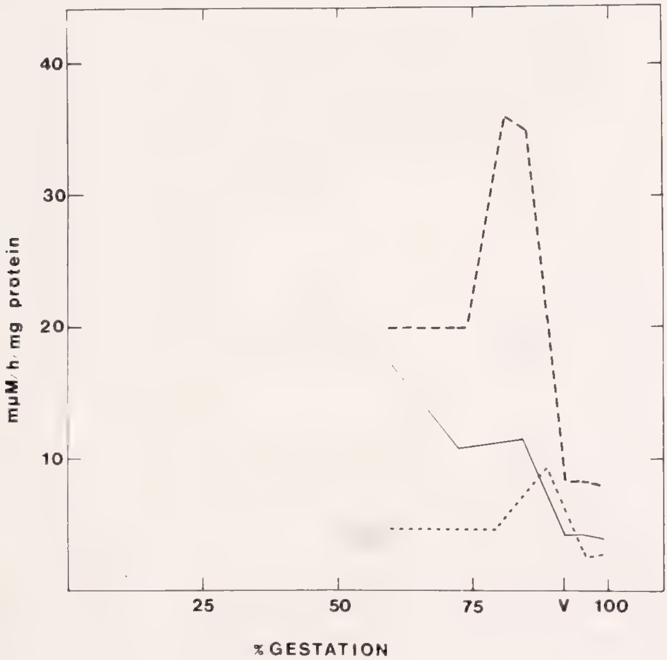

FIG. 3. Activity of lecithin synthesis enzymes of fetal rabbit. Incorporataion of CDP-(1,2-^{14}C) choline—and (^{14}C-CH$_3$)-S-adenosyl-L-methionine- - - -into Lecithin, and CDP-(1,2-^{14}C) ethanolamine- -into phosphatidylethanolamine. From Gluck et al (34).

represents the product of the CDP-choline pathway. The other relevant information in this rabbit research was the demonstrated sensitivity of the methylation pathway to pH with almost complete cessation of activity at pH 6.8 and 7.0.

Thus, in the rabbit both methylation and CDP-choline pathways are operating. While the CDP-choline path declines in activity, the other paths reach their peaks dramatically, one or two days prior to the sudden release of surface active material and viability of the fetus.

Gluck's group has also done the most definitive work exploring lecithin synthesis in man (36). By studying lung effluent, pharyngeal aspirates and alveolar lavage, the quality and quantity of lecithin synthesis were analyzed. In addition to the use of labeled substrate incorporation and the identification of PDME as an intermediate of the methylation pathway, Gluck asserts that the B-saturated fatty acid in lecithin from the methylation pathway is myristic acid rather than palmitate, and that this offers another criterion by which to measure the methylation path. Although the B-myristic has not been confirmed by most workers who find from trace amounts to 5% myristic in lecithin (37, 38, 39), Gluck's findings are, in general, dependent on substrate studies and PDME in addition to the analysis of fatty acids. The essential points are the following:

1. The CDP-choline path, which first becomes significant at 18–20 weeks, precedes methylation path activity in man as in the rabbit. It appears to stay at a low level or actually diminish in activity until week 36–38 when it begins to contribute markedly to surfactant synthesis.

2. In contradistinction to the rabbit model, where methylation appears relatively late in gestation and contributes, at least in quantitative terms a minor fraction of surface activity, the methylation appears by week 22–24 in the human fetus and contributes the greatest fraction of lecithin until term.

3. In the normal neonate the proportion of myristic acid to palmitate in the B position decreases from 7:1 at 34–36 weeks to 1.2:1 at 40 weeks. By 12–24 hours postpartum the ratio is almost 1:1 indicating a relative increase in CDP-choline activity or the release of already synthesized CDP-choline lecithin. The quantity of PDME tends to correspond with the fatty acid analysis.

4. The methylation enzyme is inhibited by conditions of acidosis and hypothermia.

While the study in humans lacks the continuous monitoring of synthetic pathways which was possible in the rabbit, the general indications are that the methylation plays the most important role until 36–38 weeks, when the CDP-choline path begins to contribute substantially, either through an increase in activity or through the release of stored surfactant.

The limitations in surveying the human fetus and the resultant lack of knowledge of intracellular storage, binding and release, make it difficult to evaluate the mechanism by which surfactant concentrations are mediated in man. Whether the CDP-choline is indeed inactive from weeks 20–38, although it appears first, or whether its product forms an exclusively intracellular pool which is not apparent in the alveolar lavage has yet to be determined. If both the rabbit and man do produce two types of lecithin which distribute selectively, as the data seem to suggest (the methylation pathway giving rise to active surfactant relatively early in man and later in the rabbit, and the CDP-choline path contributing exclusively to an intracellular pool until late in gestation in both species), the only difference between the two models is a quantitative one stemming from earlier activation of the methylation in man, allowing earlier gestational survival.

Respiratory Distress Syndrome

RDS, termed a "disease of development" by Gluck (35) has been well characterized by its early tachypnea, cyanosis, expiratory grunting, chest wall retractions and atelectasis, its tragic 20–40% mortality and the respiratory sequelae of the syndrome and its therapy in those who survive (40, 41). The syndrome's main determinant is prematurity. It has never been described in anencephaly (42).

With the first breath, a negative intrathoracic pressure of 70 cm. H_2O is developed and the normal full-term lung retains approximately 40% of the total lung volume as residual upon expiration (43). This retained volume makes the work necessary to inflate the lung on subsequent breaths considerably less. The lack of collapse of the alveoli with the first expiration is a measure of alveolar stability. The primary function of the surfactant, according to the spherical model and most current thinking, is to prevent the alveolar collapse with the first expiration. If the alveoli do collapse, every breath must develop the high inspiratory pressure of the first breath. The pattern of collapse which results from air flowing from small alveoli to large, when coupled with the physiologic right-to-left shunt caused by perfusion of collapsed lung, characterizes the ventilation-perfusion abnormality of RDS.

The first demonstration (1958) that the inability to reduce surface tension was associated with RDS was conducted by Avery and Mead (44). Using the Langmuir-Wilhelmy balance, as had Pattle (45) and Clements and Brown (46) when they originally proposed a surface tension-reducing agent in pulmonary bubbles, Avery and Mead demonstrated that the lowest surface tension (S.T.) achieved in the lung tissue of premature infants was higher than the minimum S.T. achieved in term neonates. The minimum S.T. was the highest in premature infants with RDS. Work by Brumley, Avery and Hodson (47) almost a decade later, a decade in which lecithin was identified as surfactant, was better able to describe a specific population with RDS. RDS infants had a significantly lower birth weight, younger gestational age, lower concentration of phospholipids, and higher pulmonary surface tension than infants dying of nonpulmonary causes. The RDS infants died between 5 and 72 hours after birth with a mean age of 24 hours. This study and one in lambs of varying gestational age (48) made clear that alveolar stability, increased distensibility, and minimal surface tension achieved were strongly associated with increasing concentrations of phospholipids. However, Pattle's work with pulmonary foam stability still represents the only example of in vivo surfactant function.

Gluck has proposed the most widely accepted pathophysiological mechanisms of RDS. Based on his observation that the pH and heat labile methylation path provides most of the lecithin in the pre-36 week neonate, Gluck has suggested that hypoxia, acidosis, or hypothermia, to which the premature infant is especially sensitive, may inhibit the methylation path and initiate RDS. The difficulty in differentiating between these three factors is that they are all intertwined. Hypothermia, for example, has been advanced as a possible etiologic cause of RDS. Premature infants when exposed to cold must maintain body temperature through an increase in metabolism and respiration. However, in a compromised infant, body temperature cannot be maintained, and, with the drop in body temperature, there is a rise in non-esterified fatty acids mediated by norepinephrine release (49). Gluck has postulated that the increased NE levels compete for methyl groups and might inhibit the methylation path. (This seems an improbable mechanism considering the universality of methionine as a methyl donor.) Moreover, recent work which places the level of control of methionine concentrations with the methionine-activating enzyme, indicates that this enzyme increases from week 26 to term and has a broad pH activity range (50). The increase in norepinephrine also mediates pulmonary vasoconstriction which could lead to hypoxia and acidosis. Also, hypothermia leads to acidosis through a hypoglycemic mechanism (51).

Chu considered RDS a type of pulmonary hypoperfusion initiated by the reflex vasoconstriction of an immature circulatory system (52). This vasoconstriction caused a centralization of volume with preservation of cerebral and cardiac flow while the lung, with the still patent ductus arteriosus, was excluded from its blood supply. The difficulty in accurately defining the primary etiologic mechanism of RDS is probably a reflection of the diversity of this syndrome.

In the midst of this controversy, the enthusiastic welcome accorded the revelation that the amniotic concentration of phospholipid or lecithin sphingomyelin ratio was indicative of fetal lung maturity and could be used to determine fetuses at risk of developing RDS, is easily understood (53–57).

RDS and Adrenocortical Function

Based on the observed prolonged gestation in human anencephalics and in lambs and cows with pituitary abnormalities, Liggins (58) investigated the role of the pituitary-adrenal axis in parturition. In the course of his investigations, which demonstrated that the hyperfunction of the adrenals was associated with premature parturition and could be duplicated pharmacologically, Liggins noted that lambs treated with betamethasone in utero appeared to have aerated lungs at an earlier gestational age than expected. Liggins explained these results as a demonstration of induction of precocious activity by the glucocorticoids.

The role of steroids in the RDS was advanced by Naeye et al (59) who examined postmortem adrenals from infants with RDS and control neonates. They observed a 19% decrease in adrenal size due to a reduction in the number of cortical cells in infants who had expired with RDS. In addition, 14 anencephalics were noted to have greatly reduced fetal and adult cortical zones. The authors speculated that a deficiency of steroids led to decreased surfactant synthesis and RDS. The observation that anencephalics who do take the first breath have not been observed to develop RDS was not discussed by the authors.

Reynolds challenged the view that adrenal hypofunction, at least postnatally, was a factor in RDS (60). He measured serial levels of serum cortisol in neonates with RDS and normal prematures and found that the levels were higher in RDS infants. The RDS infants also responded normally to trophic hormones. Although the kinetics remain controversial, the seemingly unimpeded passage of cortisol through the placenta in utero makes an in utero effect difficult to envision.

Glucocorticoid Treatment

It should not be surprising that the recommendation to use glucocorticoids as inducers of surfactant synthesis evolved out of Liggins' work with lambs and premature parturition and had replacement therapy as its theoretical basis.

DeLemos, Avery, Kotas, and others (61) infused hydrocortisone into fetal lamb at 110–130 days gestation for 1–6 days to qualify the effect on the lungs which Liggins had noted. Parturition occurred after 1–6 days of treatment and while none of the lambs lived more than 12 hours, the treated lungs held approximately twice the volume of air at peak distending pressures, retained significantly greater volume of air on deflation, and had a minimum surface tension less than one-half the value in controls. The authors claimed on the basis of these results that "it is clear the induction of surfactant has occurred." The increase in peak distensibility of the lung noted by the authors cannot be ascribed to any quality of surfactant described in the literature to date. Most papers reviewed by me include increased distensibility as one of the criteria with which to judge surfactant induction. One would not expect an increased volume of air with peak distention unless there was some histologic alteration or change in elastic property. The time course of most of these experiments precludes histologic differentiation as the mechanism.

Kotas and Avery performed similar experiments with fetal rabbits and 9-fluoroprednisolone (62). The lungs of all the steroid-treated rabbits were advanced by 2–4 days over their gestational counterparts based on the same criteria used in the lamb study. Since Avery and Kotas were unable to substantiate these changes on the basis of surfactant induction alone, they proposed that glucocorticoid administration had accelerated cellular differentiation. They also suggested that a decrease in the weight of the lung might indicate that the differentiation had occurred at the expense of growth. This finding was later given credence by the histologic work of Carson (63).

In 1972, Liggins and Howie conducted a controlled trial with betamethasone in mothers with threatened delivery prior to 36 weeks (17). The stated experimental support for this study was based on Liggins work with premature parturition (58), Kotas and Avery's rabbit experiments (62), and Naeye's description of small adrenals in RDS infants and anencephalics (59). Betamethasone (0.6 mg) was given I.M. to mothers at 24 hour intervals while controls received small amounts of hydrocortisone acetate on a double blind basis. Full treatment was 2 injections. The neonates whose mothers received full treatment, especially the 26–32 week infants, showed a marked decrease in incidence of RDS with glucocorticoid therapy. The authors interpreted these results to signify that glucocorticoids accelerate lung maturity in human fetuses as it does in rabbits and lambs, without a detrimental effect on mother or child.

The authors noted that serial amniotic samples in a small group of treated mothers gave no consistent change in lecithin/sphingomyelin ratio with treatment. However, work by Spellacy et al in 1973 showed that amniotic L/S values of mothers 28–32 weeks pregnant who were treated with dexamethasone for a period of 2 weeks were increased over controls (64).

Baden and associates administered hydrocortisone and placebo postnatally to infants with RDS and found no significant difference in outcome for the steroid-treated infants (19). This report essentially contradicted the work of Provenziano (65), Helwig (18), and Altman (66), all of whom found benefit in the postnatal use of steroids. Since Baden's report represents the largest population of RDS infants studied with postnatal treatment and controls, it seems probable that this mode of treatment is only minimally efficacious, if at all.

The only biochemical investigation of the inducibility of the enzymes involved in lecithin synthesis was conducted by Farrel and Zachman in premature rabbit fetuses (67, 68). The fetuses were injected at 23–24 days gestation with 9-fluoroprednisolone as described by Kotas and Avery (62). The enzyme phosphorylcholine glyceride transferase (PCGT) was shown by labeled incorporation studies to increase at 6, 24 and 72 hours after steroid treatment while the enzymes of the methylation path did not increase. This enzyme system differed from other inducible systems in that it was inhibited by cyclohexamide, placing the level of control at translation, and was stimulated by actinomycin-D. Such a paradoxic effect of actinomycin-D was previously described by Tomkins in tyrosine aminotransferase in rat hepatoma culture (69). Tomkins posited that the steroid was bound to a repressor of translation and also prevented degradation of mRNA to explain the post-transcriptional induction mechanism. Superinduction represented the actinomycin-D inhibition of synthesis of the repressor which subsequently freed mRNA for rapid translation.

Alternatives and Conclusions

Farrel and Zachman have demonstrated that at least one enzyme (PCGT) involved in surfactant synthesis in the fetal rabbit is inducible according to acceptable biochemical criteria. It thus appears that induction processes may very well play a role in the prevention of RDS by steroids. However, until the controversy surrounding the anatomy of the alveolus and the physiological function of surfactant is resolved, the importance of that role will remain obscure.

The questions which must still be answered in order to formulate a pathophysiologic hypothesis that will adequately encompass the experimental data are the following: 1) if the commonly accepted models of alveolar structure and of surfactant function are not realistic, what alternatives can be offered and what interactions might glucocorticoids have in such a model to prevent RDS? 2) What possible steroid effect might account for the increase in peak pressure volume in the lungs of steroid-treated fetuses?

Alveolar Structure: The most complete analysis of geometric considerations was presented by Weibel (31). He viewed the alveoli as lateral outpouchings surrounding the alveolar duct like a sleeve. The single alveolus did not represent the configuration found in vivo; the packing of numerous respiratory units one against another like a honeycomb, provided a more realistic picture. While the assumption that the alveolar outpouching is a sphere makes surface-volume coefficient calculation easier, Weibel appears to regard an irregular polyhedron as the most likely shape for the alveolus. It is then possible that expansion and contraction of the lung volume occurs through an angular change rather than a strict decrease in radium. If this angular model is a realistic one, the function of surfactant is alveolar stabilization becomes suspect.

Surfactant: Scarpelli clearly states the alternative functions which surfactant might fulfill physiologically (32). A complete review is not possible here, but some mention should be made of surface tension effects which might be operative in a nonspherical model.

1) Hypophase surfactant is that surfactant associated in micelles and considered to be the source of fresh, active surfactant both with polar and nonpolar sites exposed. The hypophase fraction, as well as the pulmonary surface surfactant, contribute significantly to the viscosity of the alveolar and bubble surfaces. With the addition of ions, which bind polar layers of surfactant together, the viscous forces exerted by the surfactant become considerable. This two dimensional membrane can act, as Blank has suggested (70), to resist alveolar collapse. In addition, the viscous forces which are generated by the formation by phospholipidionic bonds, increase with compression. As alveoli surface area is compressed with expiration the development of increased surface viscosity might resist further deformation.

2) Another possible function advanced for surfactant is in the regulation of capillary perfusion. The suction effect produced by alveolar surface tension might be transmitted to the pericapillary area and influence the perfusion of the local area. A significant increase in surface tension in the absence of surfactant might increase capillary flow and result in the segmental congestion commonly seen in the RDS lung for which no pathophysiologic significance has been found (71).

3) The other possible role for surfactant function which remains the only in

vivo example of its action, is in the stabilization of pulmonary bubbles. Whether these bubbles are important in pulmonary function is unknown, but their stability depends entirely on the presence of surfactant.

Glucocorticoid Effect: It is clear that glucocorticoids have multisystem effects and that more than one effect may be active in the lung. Some of the glucocorticoid-caused changes are examples of inductive processes. The two parameters which might be examined for a steroid effect, in addition to lecithin synthesis, are pulmonary circulation and the elastic quality of pulmonary structures. The former has been implicated as the site of primary pathophysiology in RDS by those workers not accepting surfactant deficiency as the initiating mechanism, and the latter must be altered to account for the observed increased peak distensibility of steroid-treated lungs.

Two enzymes shown to be inducible with glucocorticoids might be relevant to consider with regard to pulmonary circulation. Phenethanolamine methyltransferase (PNMT) (13) and methionine S-adenosyltransferase (methionine-activating enzyme) (72) have been shown to be inducible with glucocorticoids. While the effects of markedly increased epinephrine norepinephrine levels on the immature pulmonary circulation have not been described, they could be significant.

Glucocorticoids have been shown to alter the rate of collagen synthesis and degradation in several systems. Betamethasone acts on inflamed tissue, such as carrageenin granulomas, in 4–5 hours by decreasing incorporation of H^3 proline (73). This appears to be a selective effect on synthesis of collagen since total protein synthesis is not decreased. In rat hepatic cells, cortisone acetate causes a reduction in neutral soluble collagen in 2–4 days by two mechanisms (74). Intracellular collagenase activity is increased. Also, the extracellular collagenolytic activity is increased through glucocorticoid induction both in rat liver (79) and skin fibroblasts (76). This induction is accompanied by an increase in RNA precursor uptake which Hirayama's group has interpreted as a transcriptional control (74). If a similar collagenolytic effect could be demonstrated in the lung, it might explain the increased distensibility of that organ after steroid treatment. Whether this effect alone could cause the improved outlook for RDS susceptible fetuses, or whether it is associated with the widely accepted surfactant effect must be investigated.

Induction represents the mechanism of differentiation, the control system of mammalian gene expression, that we best understand. However, the irregularity of our understanding of the physiological and pathophysiological features of the lung must temper the assertions we make to explain observed phenomena. This review has sought to draw the historic chain of associations which have implicated, correctly or not, surfactant in lung function, corticosteroid deficiency in the pathophysiology of RDS, and glucocorticoid "replacement" for the prevention of RDS. The importance of the role which induction plays in the prevention of RDS will be better understood when a more clear view of the pathophysiology of RDS and the multisystem effects of glucocorticoids is attained.

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NEUROLOGIC NOTES

JOHN LUSINS, M.D., EDITOR

A Guillain-Barré Variant: Ophthalmoplegia, Ataxia and Areflexia*

Submitted by

MICHAEL J. DAVIS, M.D.

The wide spectrum of deficits seen in the course of acute idiopathic polyradiculoneuropathy (AIP) or Guillain-Barré Syndrome (GBS) is well documented (1, 2, 3, 4). The specific occurrence of total bilateral ophthalmoplegia with severe ataxia and areflexia is an uncommon event, and most likely represents a variant form of acute idiopathic polyradiculoneuropathy (5). This interesting variant is illustrated in the following case history.

Case Report

A thirty-one-year-old man was in excellent health until September 3, 1974, when he developed cough, sore throat, "tender glands" in the neck, generalized malaise, and diffuse myalgias. Four days later he noted pins and needles sensations in the fingers and toes, unsteadiness of gait, varying horizontal and oblique double vision in all directions of gaze, and intermittent vertical oscillopsia.

On admission to the Bronz Veterans Administration Hospital one week after onset of symptoms (September 10), the vital signs and general physical examination were unremarkable. The mental status was entirely normal. Speech was fluent and clear. There was mild bilateral ptosis, left slightly more than right, with weakness of left lid closure as well. Abduction of the eyes was impaired bilaterally, left more so than right. Optokinetic nystagmus was present in O.S. alone when the striped tape was moved horizontally from right to left, and in O.D. alone when the tape was moved from left to right. Tape movement in the vertical plane induced pursuit without nystagmus. The corneal reflexes and Bell's phenomenon were intact. The pupils were mildly anisoric (O.S. 4 mm, O.D. 3 mm), slightly irregular, and sluggishly reactive to light and accommodation. The discs were well marginated and fundoscopy was otherwise unremarkable. Visual fields were full to finger and red-match confrontation. Other cranial nerves were intact.

There was no motor weakness. The deep tendon reflexes were absent, except for trace right tricep and left ankle jerks. The plantar responses were flexor, and abdominal reflexes could not be elicited. Sensation was preserved. Slight intention tremor was noted on finger-to-nose and heel-to-shin testing. The gait was broad-based and unsteady with poor tandem.

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* This work was supported by Grant NS 05072.

Oculomotor deficits progressed rapidly, such that by the sixth hospital day there was complete ophthalmoplegia (Fig. 1). There was no response to attempted convergence, forced lid closure, striped tape movement, caloric stimulation, or intravenous Tensilon administration. The pupils were equal, and

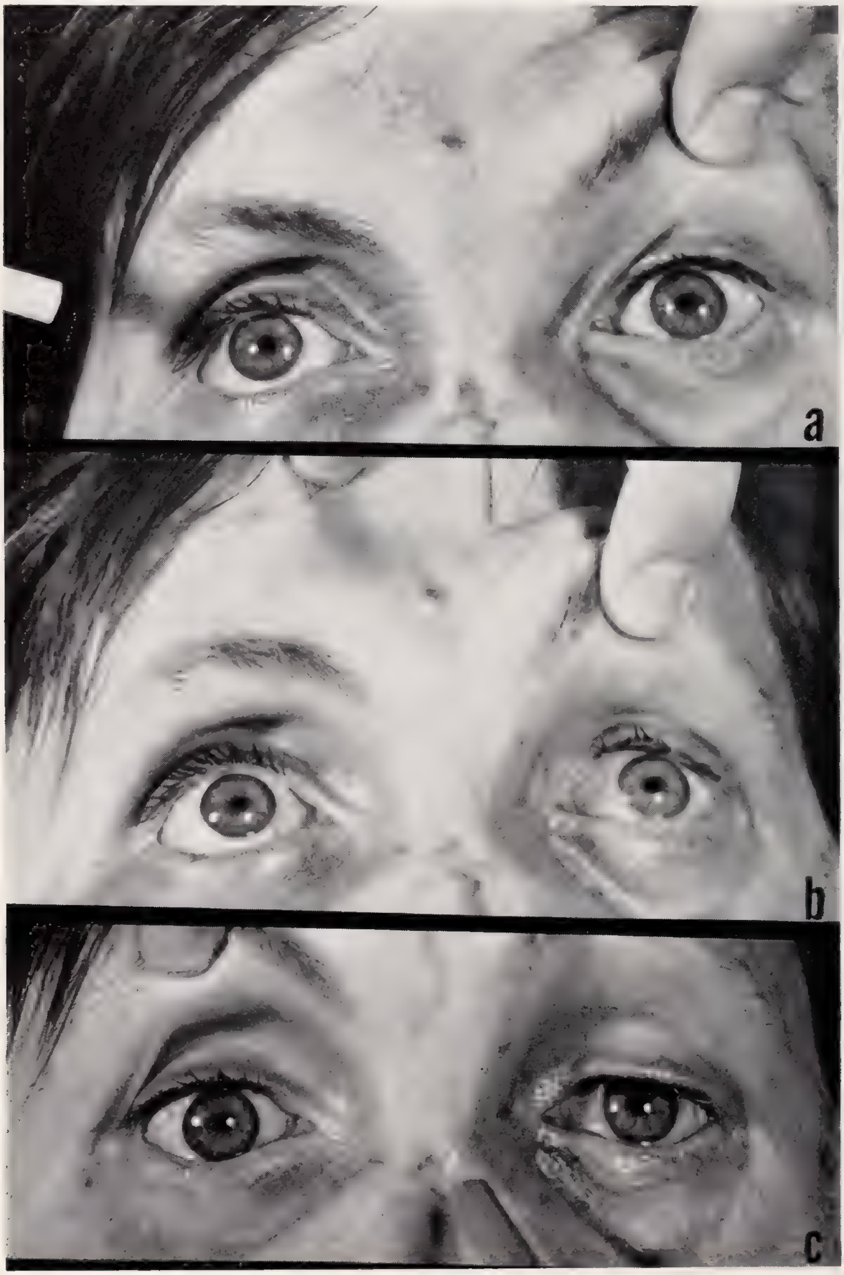

FIG. 1a. Attempted right lateral gaze; 1b. Attempted upward gaze; 1c. Attempted convergence.

continued to react sluggishly to light. Visual field perimetry and slit-lamp examinations revealed no abnormalities. There was left upper and lower facial weakness. Speech remained normal. Marked intention tremor and dysmetria became evident on finger-to-nose and heel-to-shin testing, left more than right, with dystaxic rapid alternating movements and impairment of check. Sitting up resulted in prominent head and truncal titubations. Gross ataxia prevented maintenance of the standing position.

Laboratory: Results of complete blood count, ESR, routine chemistries, T-3 and T-4 levels, serology, urinalysis, chest and skull roentgenograms (including orbital tomography) were normal. Cold and heterophile agglutinins were negative. Transient right bundle branch block was noted on EKG. Routine bacterial, fungal and AFB cultures were negative. No viruses were isolated. Acute and convalescent paired serum and CSF showed no significant viral antibody titers. Brain scan was negative. Serial CSF studies were as follows: September 10, o.p.—150 mm with 4 lymphocytes and protein of 42 mg %; September 12 o.p.—120 mm with 8 lymphocytes and protein of 35 mg %; September 19, o.p.—125 mm with no cells and protein of 141 mg %; September 24, o.p.—160 mm with no cells and protein of 157 mg %; October 11, o.p.—140 mm. with no cells and protein of 244 mg %. At the time protein was 35 mg %, CSF protein electrophoresis was normal, but immunoelectrophoresis revealed a moderate elevation of IgG at 8.4 mg %; no detectable IgA or IgM. Serum total protein was 6.8 gm % with normal protein and immunoelectrophoretic patterns. EMG studies on September 30 and October 15 disclosed denervation potentials in the left seventh nerve distribution. Decreased motor nerve conduction velocity and action potential amplitude in the left peroneal nerve were noted as well.

Course: The patient followed an orderly sequence of recovery. Facial weakness and dystaxia improved markedly by the fourth hospital week, and full ambulation was soon regained. Tricep, brachio-radialis, and achilles reflexes could subsequently be obtained with reinforcement. On the last examination, ocular movements were complete, except for mild bilateral abduction weakness. The patient was discharged on October 30, to be followed in the Neurology Clinic.

Case Analysis

The case presented displayed the following features: 1) acute, bilateral symmetrical ophthalmoparesis progressing to total external ophthalmoplegia, with a minimal element of internal ophthalmoplegia; 2) facial paresis with no other cranial nerve dysfunction; 3) severe ataxia of the cerebellar type, with no evident limb weakness or sensory impairment; 4) generalized areflexia; 5) CSF protein and IgG elevation; 6) electrodiagnostic evidence of peripheral nerve involvement; and 7) a benign course.

Discussion

Although first alluded to by Collier in 1932 (6), and subsequently discussed by other European authors, it was not until Fisher's report of three cases in

1956 (7), that the syndrome of ophthalmoplegia, ataxia and areflexia was described in the English literature. The addition of 11 cases by Elizan in 1971 (5) further established the syndrome as a distinct entity and underscored its relationship to acute idiopathic polyradiculoneuropathy (AIP). Complete recovery within weeks to months was a conspicuous feature in these and in the several interim cases reported (8, 9, 10).

Compared with the frequent involvement of other cranial nerves in AIP, marked ophthalmoplegia is generally a rare phenomenon. In six of the larger review series gathered between 1949–1969 (2–4; 11–13), 280 patients with Guillain-Barré Syndrome (GBS) were found to have cranial nerve deficits. Only four had total bilateral ophthalmoplegia, and of these, all were associated with respiratory paralysis and fatal outcomes (2, 13). None of these four had ataxia.

Histopathologic analysis of the available necropsy material from these cases with cranial nerve involvement showed selective changes in cranial nerves three, four and six, identical to those seen in the peripheral nerves of more typical GBS. The lesions consisted of focal perivenular mononuclear infiltrates, corresponding zones of myelin and axonal breakdown, and Schwann cell proliferation. The findings tended to be variable among the three nerves and, at times, could only be partially correlated with the clinical deficits. In the one case reported with positive brain stem pathology (14), the nuclear abnormalities of three, four and six were felt to be secondary to distal Wallerian degeneration.

The striking feature of gait and limb ataxia without significant motor or sensory impairment has remained unexplained. Perhaps, as Fisher first postulated (7), it results from "a unique, widespread, and selective attack on sensory neurons underlying postural adjustments." More directly, Richter (15) found no brain stem or cerebellar alterations, but noted posterior root lesions with secondary loss of myelinated fibers in the dorsal columns and spinocerebellar tracts. In this way, the ataxic form of AIP was said to be peripheral nerve demyelination.

The similarity between GBS and experimental allergic neuritis in rabbits was first indicated by Waksman and Adams in 1955 (16). Subsequent studies suggested that the disease is produced immunologically, either by a circulating myelinotoxic IgM antibody (17–19), or by a cell-mediated process of delayed hypersensitivity (21–23).

The quantitative increase in CSF IgG in the present case is of considerable interest. CSF concentrations of IgG, IgA, IgM, and other protein fractions have all variously been reported to be elevated in AIP (24–28). The highest concentrations have occurred in CSF specimens with the highest total protein levels, and in those analyzed early in the course of the disease. Early immunoglobulin elevation at a time when total protein was well within normal range suggested to Dencker (24) that the immunoelectrophoretic pattern of CSF protein may be of greater diagnostic value in AIP than total protein or protein-electrophoretic determinations alone. Conversely, CSF immunoglobulins have been noted to become normal almost linearly with clinical improvement, even when total protein levels remained quite elevated. No consistent correlations have been drawn with the serum protein and CSF immunoglobulin profiles in patients with AIP (27). Perhaps, as Hartley pointed out (25), the factors controlling the CSF immunoglobulins operate independently of the other major proteins. Specific disruption of normal CNS transport mechanisms or local overproduction in the CNS have been proposed (25, 28).

Summary

An additional case of acute-onset, total bilateral ophthalmoplegia, ataxia, and areflexia is described. The alarming clinical onset is seen to belie the benign nature of the illness. The syndrome would appear to be a transitional form of acute idiopathic polyradiculoneuropathy.

Acknowledgment

The author wishes to thank Drs. E. A. Weinstein and F. Sherman of the Bronx Veterans Administration Hospital for their assistance.

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UNUSUAL PROBLEMS IN SURGERY

Bochdalek Hernia Presenting at One Year of Age

A. ROBERT BECK, M.D. EDITOR

Diaphragmatic hernias through the foramen of Bochdalek are usually seen in the newborn period. Although several series of cases include patients in whom the diagnosis was first made in early childhood (1, 2, 3), it must be assumed that a diaphragmatic hernia was present at birth. In many of these children, a sac, limiting the size of the hernia, was present. In the following report a child with a previously normal chest x-ray subsequently developed a symptomatic Bochdalek hernia.

Case Report

A 3,300 gram female was delivered after a normal 40 weeks' gestation. The mother was a 34-year-old white para 5-0-3-4. Labor and delivery were uncomplicated. The child had an apgar score of 10. The infant was noted to have gross facial asymmetry, narrowing of the right palpebral fissure and a hypoplastic left ear. Examination of the chest revealed good air exchange bilaterally. There was a Grade II blowing systolic murmur heard along the left sternal border. The remainder of the physical examination was within normal limits. Roentgenograms of the chest showed that the lung fields were clear and the heart was probably enlarged in its transverse diameter (Fig. 1). There was a deformity of the dorsal and lumbar spine with hemivertebra at T-6, T-9, and L-1. Intravenous pyelography revealed a non-fused crossed ectopia with both kidneys on the right. An electrocardiogram suggested the presence of right ventricular preponderance. Neurologic examination was within normal limits. Despite apparent adversities, the child did well and was discharged at one month of age.

The child was seen in the Outpatient Department and was doing well except for slow weight gain and general growth retardation. At five months of age, she weighed 9 lbs. 14 oz. Chest x-rays were taken on several occasions. All showed normal lungs and no evidence of a diaphragmatic hernia.

At one year of age, the child was admitted to the hospital in severe respiratory distress. Approximately one week prior to admission, she developed a mild upper respiratory infection. On the evening prior to admission, she was severely dyspneic. It was noted that she became cyanotic when lying down and that her dyspnea was somewhat relieved when sitting up. Her pulse rate was 164 beats per minute, her respiratory rate was 80 per minute, and her temperature, 98.6°. Her neck veins were distended. Examination of the chest revealed subcostal

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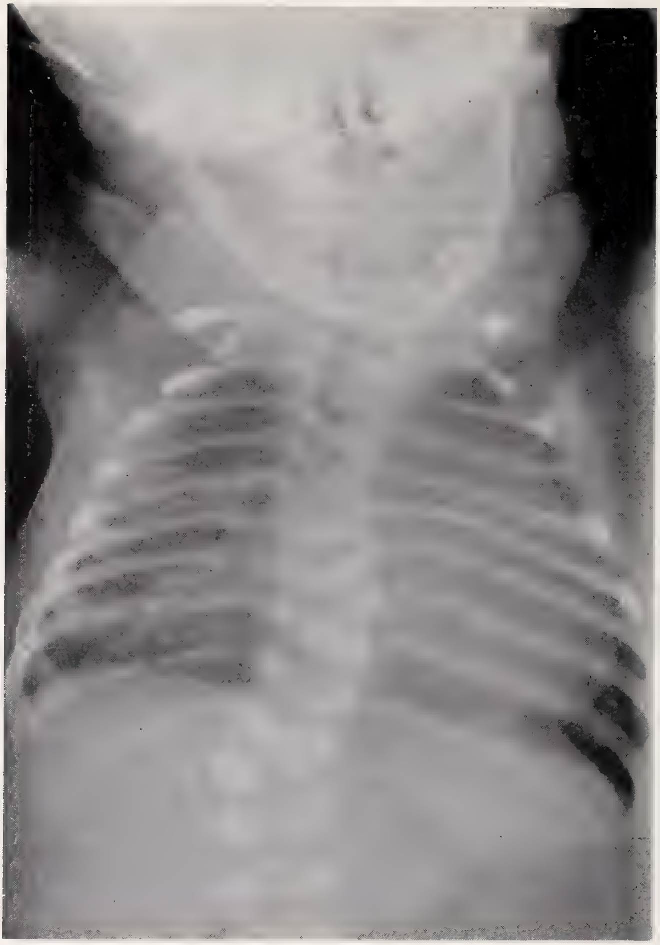

FIG. 1. Chest x-ray at one month of age. There is no diaphragmatic hernia seen.

and intercostal retraction. Bilateral crepitations were heard. The heart rate was rapid and a Grade III systolic murmur was heard. The remainder of the examination was within normal limits. Shortly after admission, the child had a respiratory arrest from which she was successfully resuscitated with endotracheal intubation and the administration of oxygen. An intravenous cutdown was performed and nasogastric tube was inserted. A chest x-ray revealed what appeared to be a large right Bochdalek hernia with bowel filling the entire right hemithorax and a marked shift of the heart to the left (Fig. 2). Since the child had had several normal chest x-rays in the past, and despite her poor condition, gastrografin was inserted into the nasogastric tube and an x-ray was obtained. This film confirmed the diagnosis of a large right posterior-lateral diaphragmatic hernia (Fig. 3) and she was immediately taken to the operating room. Surgery was performed under general anesthesia using a right sub-costal in-

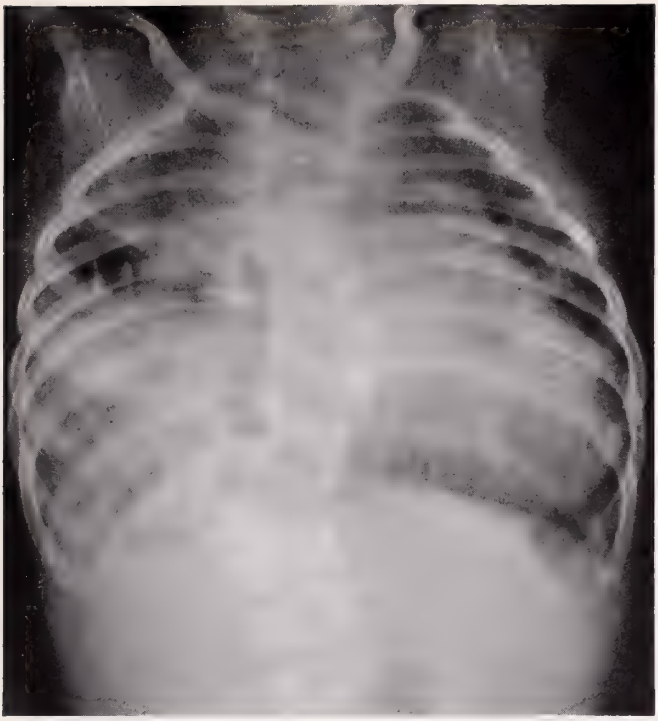

FIG. 2. Chest x-ray at one year of age. Note right Bochdalek hernia.

cision. It was noted that the entire small bowel and the right colon occupied the right thoracic cavity. The liver was displaced anteriorly, and the bowel had passed behind it through a 2 × 1 cm. defect in the posterior-lateral portion of the right hemidiaphragm. After retracting the liver downward and medially, a rubber catheter was inserted through the defect and the bowel delivered from the chest. No hernia sac was present. The defect was closed using two layers of 2-0 interrupted silk sutures. Further exploration revealed the presence of numerous bands across the duodenum associated with malrotation of the colon. The duodenal bands were divided and a gastrostomy was performed. The abdomen was closed without difficulty. A chest tube was inserted and connected to an underwater seal. The lung expanded promptly and remained expanded. The patient did well following surgery. At the time of discharge, she weighed 11 lbs. 12 oz. She gained weight rapidly and three months following surgery, weighed 16 lbs. 8 oz. At two years of age, she weighed 23 lbs.

Discussion

The late appearance of a Bochdalek hernia in this child was probably due to occlusion of the diaphragmatic defect by the liver. When the child developed a respiratory infection at one year of age, severe coughing may have displaced the liver and allowed the bowel to enter the chest through the patent pleuro-

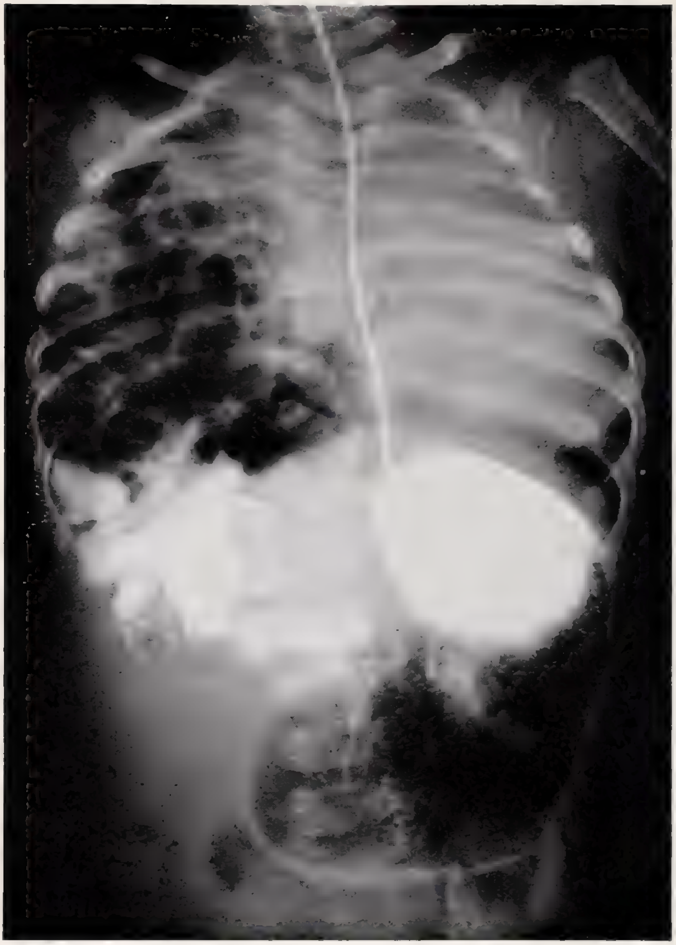

FIG. 3. Preoperative gastrografin study.

peritoneal canal. The poor weight gain prior to surgery was no doubt due to the partial duodenal obstruction caused by peritoneal bands. Following surgery and relief of obstruction, a rapid weight gain took place.

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In Memoriam

GORDON D. OPPENHEIMER, M.D.
1900–1974

Dr. Gordon D. Oppenheimer, Emeritus Professor of Urology at Mount Sinai School of Medicine and former Director of the Department of Urology at The Mount Sinai Hospital, died at Mount Sinai on December 9, 1974 of cardiac failure at the age of 74.

Dr. Oppenheimer was born in New York City on June 30, 1900. He graduated from Columbia College with a Bachelor of Science degree in 1919. He attended Columbia College of Physicians and Surgeons and received his M.D. in 1922. He served a two-year internship at Mount Sinai Hospital, completing it in 1924. During World War II Dr. Oppenheimer acted as Second in Command of the General Surgical Service at Mount Sinai Hospital. During his lifetime he actively served on the staffs of Bronx Hospital, Gouverneur Hospital, Sydenham Hospital, and The Mount Sinai Hospital. He became the Director of the Department of Urology at Mount Sinai in 1947 and remained in this capacity until 1963. He was a member of the New York Surgical Society, the New York Academy of Medicine and was a Fellow of the American College of Surgeons. A Diplomate of the American Board of Urology, Dr. Oppenheimer was a member of the American Urological Association and of the New York Section of the American Urological Association. He held memberships in the American Medical Association as well as the Medical Society of the County of New York. From January 1st, 1931, until February 15th, 1944, Dr. Oppenheimer served as a Medical Officer with the New Yory City Fire Department. In 1971 after leaving the private practice of urology, he became Chief of the Veteran's Administration Regional Office Outpatient Urology Clinic. He remained in this capacity until 1974.

While Dr. Oppenheimer made many outstanding contributions to medicine and medical literature, perhaps his most outstanding contribution was his work on regional enteritis. Dr. Oppenheimer was a member of the original team which delineated this important condition. In fact, it was Dr. Oppenheimer who worked in the laboratory and did the pathological description of the disease.

A prolific writer, Dr. Oppenheimer published sixty-nine separate contributions to the world's medical literature. The range of these contributions is remarkable, including, of course, urological subjects as well as basic science work and his work on regional enteritis. His first paper appeared in May of 1932, when he published, in association with Dr. Leon Ginsburg, in the *Transactions of the American Gastroenterological Association*, the article "Non-Specific Granulomata of the Intestines." This was followed in October of that year by "Regional Ileitis" published by the *Journal of the American Medical Association*. Additional articles on the subject appeared including one in the *Annals of Surgery* in 1933.

There followed articles on rectal blastomycosis, x-ray control in the treatment of renal calculi, jejunostomy for alimentation, x-ray control of surgery in the kidneys, the relationship between parathyroid disease and renal calculi, and other articles of urologic import. His extremely wide-ranging clinical activities enabled him to describe for the literature many unusual cases, an example being the description of an incarcerated inguinal hernia which contained a bladder cancer and recurrent, non-traumatic intraperitoneal rupture of the urinary bladder. And, of course, he published "Urological Complications of Regional Ileitis" which he wrote in 1949 with Dr. Leon Ginsburg. With Dr. Stephen Rosenak he was a pioneer in dialysis and they reported on "An Improved Drain for Peritoneal Lavage." An example of his basic science interest was "Blood Pressure of Chronic Hypertensive Dogs Surviving Bilateral Nephrectomy" which was published in 1952, with B. S. Oppenheimer and S. S. Rosenak in The Journal of The Mount Sinai Hospital.

Dr. Oppenheimer was universally liked. He was kind, gentle, humane and much sought after as a consultant. He gathered about him an excellent staff and was genuinely interested in the education of the young physicians going through his residency program. When the residents graduated, they frequently consulted with him and came to rely upon his almost uncanny clinical judgment. He was very proud of the fact that none of his residents had ever been turned down for anything for which he recommended them. Despite his immense experience and clinical judgment his demeanor was ever that of a man who was humble and who was learning, and he encouraged his staff to express their individual opinions and never forced his on them.

Dr. Oppenheimer is survived by his wife, the former Frances Reese, a son, Gordon S. Oppenheimer, a daughter, Mrs. Ann Kniffen, and four grandchildren.

LEONARD BIEL, JR., M.D.
for the
EDITORIAL BOARD

Treatment of Hemorrhoids and Application of Cryotechnique

CHANGYUL OH, M.D.

CONTENTS

I. Review of the Treatment of Hemorrhoids

- A. Surgical
- B. Nonsurgical
    - Injection
    - Ligation
    - Dilatation

II. Cryosurgery

- A. Introduction
- B. Cryodestructive mechanisms
- C. Clinical application for hemorrhoids
    - Clinical material
    - Indication
    - Preparation
    - Cryoinstruments
    - Method
    - Postoperative care
    - Results
    - Comment

I. Review of the Treatment of Hemorrhoids

Hemorrhoids are one of mankind's most common ailments, affecting approximately 50%–100% of the adult population (1–4). Surgical treatment of piles (its popular name) was one of the earliest operative procedures, practiced in ancient Greece and Rome and reported by Hippocrates, Celsus and Galen (1, 5). It is common knowledge that in most cases such surgery is extremely painful, often causing people to conceal rectal bleeding and refrain from seeking qualified medical aid, driving them instead to nostrums advertised in popular magazines, radio, and television, even at the risk of such a serious condition as cancer. If postoperative pain could be eliminated, it is likely that the patient would be more willing to seek advice regarding hemorrhoidal symptoms, thus making possible an early diagnosis, not only of hemorrhoids but of ano-rectal cancer.

Since the dawn of history, numerous investigators have attempted to im-

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TABLE I

Treatment of Hemorrhoids

Surgical:		
Hippocrates	BC 460	Ligation or Excision
Celsus	BC 25	Ligation and Excision
Galen	131	Intermittent Ligation
Lanfrank	1296	Ligation and Hot Iron
Petit	1774	Submucosal Ligation
Cusak	1846	Clamp and Cautery
Pollock	1880	Crushing
Whitehead	1882	Circular Excision
Salmon-Allingham	1888	High Ligation and Excision
Mitchell	1903	Clamp and Oversewn
Earle	1911	
Ferguson and Heaton	1959	Primary Closure
Reynold	1972	Sutureless Excision
White et al.	1972	Sleeve Resection
Nonsurgical injection:		
Morgan	1869	Iron Persulphate
Mitchell	1871	Carbolic Acid in Oil
Kelsey	1884	5–7.5% Phenol in Glycerine
Edward	1888	10–20% Phenol in Glycerine
Terrell	1917	5% Urea-Quinine
Boas	1922	70% Alcohol
Ligation:		
Blaisdell	1954	Silk
Barron	1963	Rubber Band
Dilatation:		
Copeland	1810	Bouginage
Lord	1968	8 Finger

prove techniques for hemorrhoidal treatment, yet we are still far from the ideal. Treatment is divided into two categories: surgical and nonsurgical (Table I). We shall herewith review the historical background of such therapeutic modalities.

A. Surgical Treatment

The most thorough and exhaustive historical study of the surgical treatment of hemorrhoids was conducted by Parks (5, 6) and well summarized by Goligher (1). Surgical treatment was probably initiated by Hippocrates (460 B.C.), who utilized ligation of whole hemorrhoids with or without excision or burn. Celsus (25 B.C.) described ligation and excision in *De Medicina* and discussed postoperative pain, urinary retention, and anal stenosis. Galen (131–201 A.D.) favored intermittent ligation of the pedicle in order to avoid postoperative pain and spread of gangrene. Aetius (527–565) advocated the total removal of hemorrhoids by ligation and excision. During the Middle Ages, however, progress was not maintained and the art remained at a low ebb, chiefly because it had fallen into the hands of quacks and barbers. However, during this period, Lanfrank (1296) practiced ligation and hot iron. There was little if any advance until

1739, when Heister described ligature with excision, and in 1749, when Morgagni became the first to enunciate a scientific account of the cause of hemorrhoids. In 1774, Petit condemned excision of piles because of severe bleeding and rejected ligature because of pain. He therefore modified the ligation procedure by dissecting out the skin and mucosa before transfixing the vascular pedicle.

Much has been written on hemorrhoids in the modern era, for example: double ligation and excision (Sir Cooper, 1836); clamp and cautery (Cusack, 1846); crushing the pile (Pollack, 1880); and circular resection of hemorrhoids (Whitehead, 1882) (7). These procedures still had considerable drawbacks, such as pain, infection, bleeding and anal stenosis.

Salmon (1888) and Allingham (1901) (8) introduced a superb modification consisting of making a cut with scissors at the mucocutaneous junction of the pile and stripping the mucosa-covered portion to the top of the anal canal, where it was ligated and the excess excised. This operation lessened the postoperative pain considerably but frequently resulted in anal stenosis, which led to further modifications: Miles (1919) (9), low ligation; Lockhart-Mummery (1934) (10), ligation at the mucocutaneous junction and suturing the stump at the intersphincteric septum. Mitchell (1903) (12) and Earle (1911) (13) described the procedure of clamping the hemorrhoid and excising the tuft, then oversewing it. But this was condemned by Turell (1952) (14) and modified as follows: The pile was dissected from the underlying muscle to a point above the pectinate line, then the pedicle so formed was clamped, excising the pile, and suturing it over the clamp. Parks (1956) (6) reintroduced the modification of Petit's submucosal hemorrhoidectomy: Skin and mucous covering the hemorrhoids were tediously separated underneath and the vascular pedicle ligated. The mucosal flaps fall back more or less accurately onto the raw area, except for the perianal portion, where a vent is created for free drainage. Ferguson and Heaton (1959) (15) advocated excision of hemorrhoids by elliptical incision and primary closure of the wound. Buie (1960) (2) described excision of three standard hemorrhoids and excision of the anal tag between these wounds and closure with running stutures.

Further modifications, with minor differences, are still being reported in the literature, for example, sutureless hemorrhoidectomy (the separation of the hemorrhoid and the clipping of the pile) by Reynolds (1972) (16) and a modification of the Whitehead procedure (sleeve resection of the hemorrhoid-bearing region with circular anastomosis) by White et al (17). All of the operative techniques named have aimed chiefly at the avoidance of postoperative pain but have not alleviated it to a satisfactory degree. Thus, several nonoperative, relatively painless procedures have been proposed with varying degrees of success.

B. Nonsurgical Treatment

In the main, three types of nonsurgical methods are practiced: injection, ligation and dilatation. None of these methods obtain the good results of surgical excision, although a few surgeons have claimed dramatic relief with nonsurgical methods.

Injection: This subject was well outlined by Anderson (1924) (18), Bacon (1949) (19), Gabriel (1963) (20), and Goligher (1967) (1). The main objects are: 1) constriction of the small veins and arteries in the submucosa and protection from distension of pile by back pressure and 2) production of a submucous sclerosis that will fix the mucosa to the underlying muscular coat and in turn reduce the amount of prolapse. It was first practiced by Morgan of Dublin in 1869 with an injection of iron persulphate. Since then various sclerosing agents have been used by different investigators as follows:

Morgan	1869	Iron sulphate
Mitchell	1871	One part carbolic acid with two parts olive oil
Kelsey	1884	5%–7.5% phenol in glycerine
Edward	1888	10%–20% carbolic acid in glycerine and water
Terrell (21)	1917	5% urea-quinine
Boas (22)	1922	70% alcohol

The site of injection is disputed: either into the pile or above the pile. The latter location appears to be favored, as proposed by Blanchard in 1928 (23). The success rate varies as to selection of patients or follow-up period. It is limited to the early stage of internal hemorrhoids and the recurrence rate is rather high, almost 90%, at the end of three years (24). Thus the injection method is of limited value, applicable only to internal hemorrhoids, and certainly cannot replace standard surgical procedures.

Ligation: Barron (1963) (25) described an improved modification of the ligation technique for the treatment of hemorrhoids. The technique was originally proposed by Blaisdell (26, 27) and over the years has achieved increasing popularity worldwide (28–32). The main advantages are: 1) ambulatory procedure; 2) no anesthesia required; 3) simple technique; and 4) minimal disability. However, there are disadvantages: 1) the technique is limited to nonsensitive mucosa covering hemorrhoids (internal hemorrhoids); 2) it requires ligation one at a time because of pain and is an interval procedure; 3) pain and discomfort are considerable (approximately seven to ten days); 4) it is often imperfect for patients previously treated with sclerosing-agent injections because fibrosis prevents complete strangulation.

Despite these disadvantages, the procedure is becoming popular because of its relatively good results. It differs from the injection method or dilation technique in that it eradicates hemorrhoids, as do surgical procedures. However, the absolute value in terms of cure is far less than with the surgical method (33).

Dilatation: Copeland (1810) (34) believed that hemorrhoids were caused by a hypertonic anal sphincter. Therefore he advocated rectal bouginage in the conservative treatment of piles. This was taught at many medical centers at that time, especially in the French schools, and so widely was this theory held that it must be credited with some degree of truth. Recently, Lord (35) reintroduced the forceful dilatation method and obtained good results. The hypothesis is that narrowing, caused by the pecten bands, forces blood into the hemorrhoidal plexus as the fecal mass descends, resulting in venous engorgement and eventual formation of hemorrhoids. It is, therefore, believed that disruption of this band allows decongestion of the hemorrhoids and relief of symptoms. This method was adopted by several investigators and results vary. Most investigators agree as to the relief of symptoms following this procedure, but the hemorrhoid does not disappear, and subsequent complications are not trivial (36–38). Hood and Williams (39) compared the results of dilatation versus ligation and found a 17% failure rate in the former and none in the latter.

Thus a nonsurgical procedure cannot be expected to produce a permanent cure, as with removal of the hemorrhoid either by surgical or other methods such as ligation. However, the surgical method is too painful, and ligation is limited to internal hemorrhoids and accompanied by considerable discomfort.

In 1969, however, Lewis et al (40) advocated cryohemorrhoidectomy and claimed that it was not only painless but also very effective. It has proven worthwhile to evaluate the validity of the procedure.

II. CRYOSURGERY

A. *Introduction*

The effects of cold temperature were studied nearly 300 years ago by Robert Boyle who, in 1683 (41), published a monograph entitled *New Experiments and Observations Touching Cold*. Since then numerous articles and monographs have been published on the subject of cryobiology. The most extensive and thorough bibliography was reviewed by Luyet and Gehenio in 1940 (42) which listed 382 articles. In recent years, detailed and comprehensive works about cryobiology and cryosurgery have been described by many investigators, among them Parkes in 1957 (43), Rowbotham et al (1959) (44), Meryman in 1966 (45), Hankinson in 1970 (46), Smith in 1970 (47), and Von Leden and Cahan (1971) (48). In general, early investigations were mainly concerned with conservational cryobiology, with only a few which focused on destructive cryosurgery. Clinicians, however, focused more interest on cryosurgery than basic cryobiological research. The use of cold temperatures in surgery was first documented by Arnott in 1851 (49) in the treatment of cancer. Subsequently, in 1883, Openchowski (50) was able to freeze an area of the cerebral cortex with a jet air spray of evaporatory ether. White (51) applied this technique in the treatment of skin lesions and observed gratifying results. Fay (52) applied extreme cold as a method of inhibition and destruction of substantial extensive cervical tumor and noticed relief of pain with shrinkage of mass.

Ophthalamologists were the first subspecialists to use the cold technique. Bietti in 1933 (53) and Deutschmann in 1935 (54) reported using cryogenics to produce a thermal chorio-retinitis to seal retinal tears. This was done by employing solid carbon dioxide. Freezing methods were applied only sporadically in clinical use until 1961 when Cooper and Lee (55) described a unit in which liquid nitrogen was circulated through a metal probe that was insulated except for its tip. Cooper's successful early experience with Parkinson's disease fascinated Cahan of the Sloane-Kettering Institute for Cancer Research. After hundreds of trials, Cahan (56) was convinced that he had a valuable new tool for treatment of tumors. This prompted rapid progress in cryosurgery in the fields of otolaryngology (57), ophthalmology (58), urology (59), dermatology (60), gynecology (61), proctology (40, 62) and head and neck surgery (63).

Dermatologists experienced striking success in their care of many lesions including cutaneous malignancies. Similar excellent results were obtained in the treatment of cervicitis by gynecologists. In 1969 the technique was applied in the treatment of hemorrhoidal disease by Lewis et al (40) with gratifying results which have been subsequently confirmed by Detrano (64), Williams et al (65), Barron (66), Rudd (28), and Oh and Dreiling (67).

Cryosurgery is a most dramatic and effective technique which has already achieved its niche in medicine. Since it is rapid, safe, and least disturbing to the patient's physiological integrity, it is ideally suited for poor-risk patients and permits definitive surgery for many who have minimal chances for survival under normal circumstances.

B. *Cryodestructive Mechanisms*

Although ever-increasing applications of cryosurgery in various fields have evolved over the past decade, the exact mechanisms through which living tissue is destroyed have not been clearly understood. Numerous hypotheses have been reported by various investigators on the basis of experiments either in vivo or in vitro.

In 1940, Luyet and Gehenio (42) extensively reviewed the literature, conducted exhaustive experiments and summarized fourteen possible mechanisms of cellular death or injury from low temperature. They admitted that the subject was rather controversial and could not draw any conclusions from the data gathered from the literature. Recently a number of monographs have been published regarding detailed cryodestruction. We will briefly discuss the most pertinent aspects of cryodestructive mechanisms and refer the reader to the publications of Meryman (45), Wolstenholme and O'Connor (68), Zacarian (69), Smith (47), and Von Leden and Cahan (48) for more detailed information.

Living tissues are, in essence, aqueous systems and water is the dominant component that serves both as solvent and contributor to molecular structure. During the process of freezing, these balanced distributions of water are severely modified and irreversible changes of tissue can be thereby induced. The most acceptable concepts are:

1. Chemical derangement
2. Mechanical insult
3. Vascular damage

When living tissues are frozen, theoretically there are two possibilities in terms of ice crystallization. Ice may form in extracellular space or in intracellular space. When frozen slowly, a small crystal of ice forms between the cell and as it grows larger, water is withdrawn from the cell. As a result, the cells collapse due to a sudden increased extracellular mass and sudden loss of intracellular water. Furthermore, within the collapsed cell there are highly concentrated electrolytes and marked water depletion (concentration and dehydration). The other possibility is the simultaneous freezing. In this situation, the ice crystal forms uniformly throughout the cell and causes disruption of intracellular organisms and membranes.

Other important changes occur in the vascular system. It has long been thought that frostbite coagulates the blood in the smaller vessels and eventual anoxia causes further destruction of frostbitten tissues. A number of investigators conducted direct observation of blood-flow changes in frostbitten ears or feet of rabbits (69-72). It became obvious that immediately after thawing, blood flows into all vessels of the frozen area in the early period but stasis begins to appear five to ten minutes later. The vessels dilate widely and become filled with red and white blood cells. The stasis is accompanied by loss of fluid from the capillaries into the surrounding tissues due to increased vascular permeability and the formed elements are left concentrated in conglomerate masses in the vessels. The phenomena are not caused by coagulation, since an identical picture is seen in vessels of animals whose blood has been made incoagulable by heparin injection. However, Zacarian's study shows the surfaces both of leukocytes and platelets and that of the endothelium of vessel walls become sticky and form a shower of emboli, which adhere to the vascular endothelium. Whichever it may be, stasis did occur following sub-zero cold injury and was permanent and irreversible.

We have conducted a series of experiments to evaluate the clinical course and histologic changes of extreme cold injury. Dog skin was frozen at −89° C for three minutes, three minutes twice, and five minutes. Soon after freezing the lesion became swollen and appeared hemorrhagic. The edema gradually increased and reached its maximum on the third day, accompanied by considerable discharge. The skin became mottled with pale, darkish spots, gangrenous, and separated from the underlying base with a sharp demarcation in one to two weeks. The wound healed rapidly with little scar formation by three to six weeks. The extent of tissue destruction was proportional to freezing time and repetition (Fig. 1). In other words, the longer the freezing, the more the destruction; repeated freezing results in more extensive destruction even if frozen for a short period of time.

The light microscopic view reveals diffuse edema and vascular congestion in the dermal layer. The borderline in the muscular layer shows sharp demarcation of coagulation necrosis with the intact adjacent zone (Fig. 2). Fine structural changes are noted under the electron-microscopic view (Fig. 3): 1) Soon after freezing, normal patterns of muscular structure disappear. Myofilaments are disrupted and frequently show areas of moth-eaten appearance; 2) In some areas, the sarcometric patterns are contracted; 3) Cristae patterns of the mitochondria are obscured; 4) The basement membrane cannot be distinguished from the underlying sarcolemmal membrane and is often replaced by connective tissue fibers; 5) The capillaries show swelling of the walls containing numerous small vesicles. Cross-section reveals marked expansion of interfibrillar space and an area of ruptured membrane. At a later stage (third day): 1) The sarcolemmal membrane is almost completely disrupted; and 2) Interfibrillar spaces are no

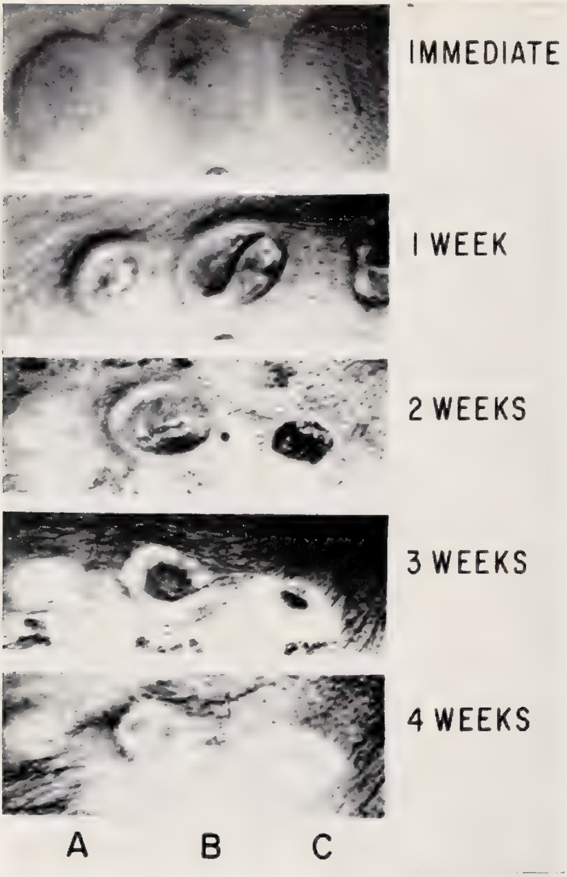

FIG. 1. Local effect of freezing on dog skin: a) Frozen for three minutes; b) Repeat freezing for three minutes; c) Frozen for five minutes (from C. Oh and D. Dreiling, Mount Sinai J Med 41:658, 1974).

longer distinguishable and are often replaced with vacuoles and electron-dense bodies suggesting lysosomal activity.

Thus, frozen tissue undergoes profound morphologic changes, such as vascular congestion, rupture of membrane, thickening of vascular wall, diffuse edema of interfibrillar space and finally necrosis. It is, therefore, fair to say that at this stage the cryodestructive mechanism is a combination of chemical derangement, mechanical insult, and vascular stagnation (Fig. 4).

It has long been debated whether −20° C is the mandatory temperature for tissue destruction or if ice-crystal formation alone is sufficient to destroy living cells. We have experimented by applying the probe to dog skin to measure the extent of ice formation and observing the clinical cause (Fig. 5). The frozen area presents uniform destruction throughout the lesion, even though the temperature drop from the center of the lesion to the periphery is very steep. The steep

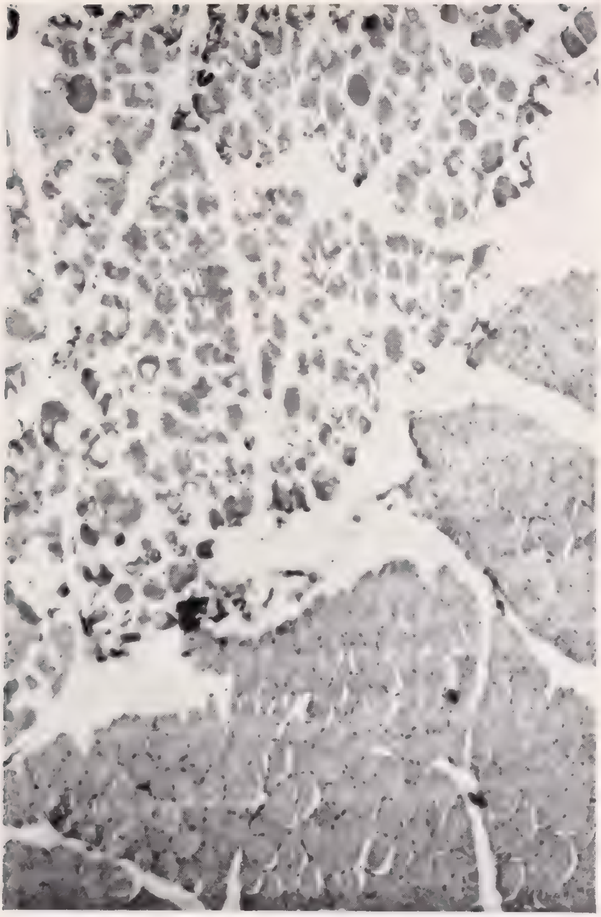

FIG. 2. Borderline of muscular layer reveals marked demarcation between the cryode structive zone (coagulation necrosis) and intact tissue.

temperature gradient is present across the frozen ice-ball with 0° at the periphery (Fig. 6). The spherical ice-ball formation is inversely proportionate to the degree of temperature, with the lateral and vertical extension of the ice-ball being almost equal (Fig. 7). In spite of 0° at the peripheral region, the uniform death of the frozen area supports the hypothesis that ischemia rather than crystallization plays the major role.

Similar studies were made for the columnar epithelium of the dog colostomy stoma, imitating the treatment of internal hemorrhoids. The stoma was frozen with liquid nitrogen and nitrous oxide simultaneously for five minutes and the clinical course observed (Fig. 8). It was almost identical to that of the skin lesion, though healing time was slightly more prolonged for the stoma. The scar formation was rather smooth and very little contracture was seen. This characteristic of cryogenic destructive power was applied to hemorrhoidal disease.

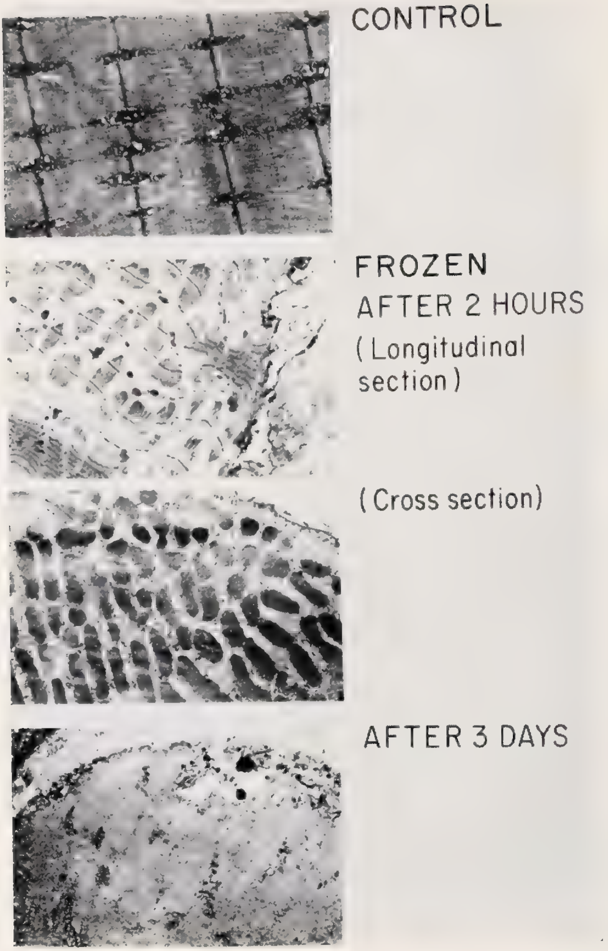
CONTROL
FROZEN
AFTER 2 HOURS
(Longitudinal section)
(Cross section)
AFTER 3 DAYS

Fig. 3

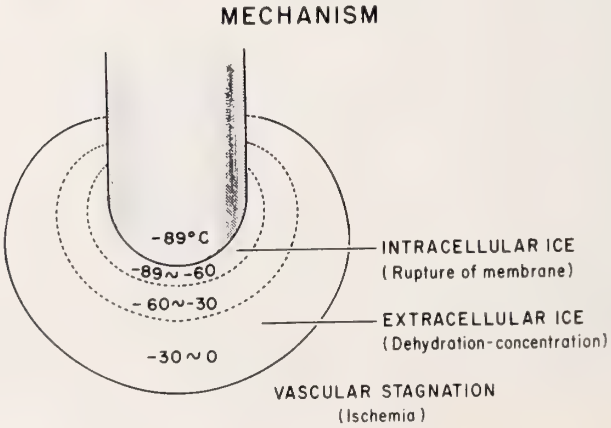
MECHANISM
-89°C
-89∼-60
-60∼-30
-30∼0
INTRACELLULAR ICE
(Rupture of membrane)
EXTRACELLULAR ICE
(Dehydration-concentration)
VASCULAR STAGNATION
(Ischemia)

Fig. 4

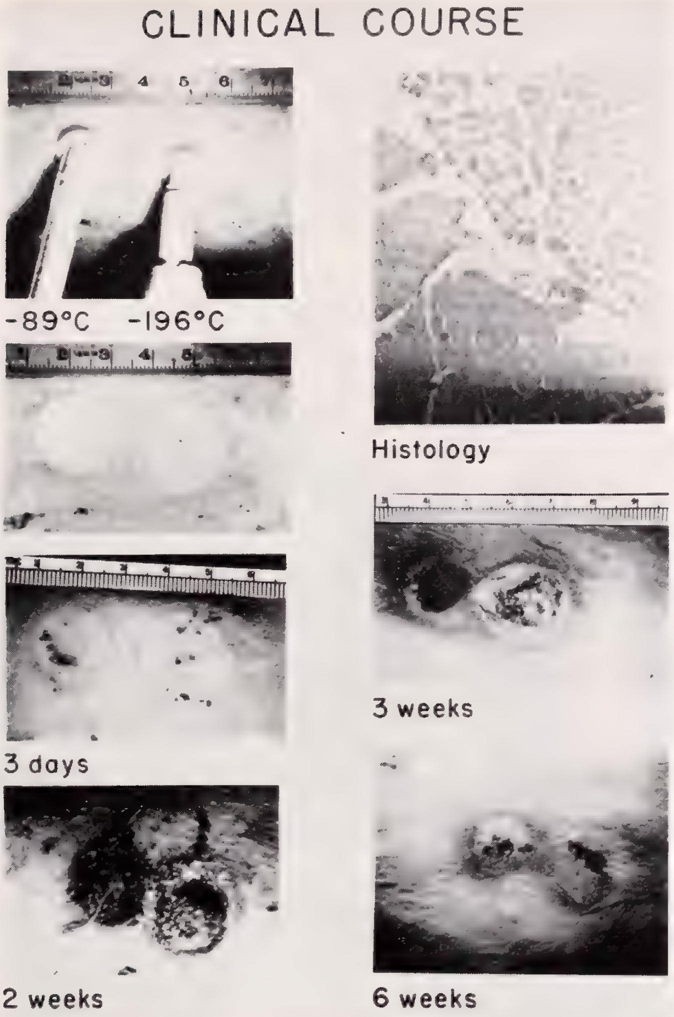

Fig. 5. The correlation between the ice formation and the destructive pattern of tissue: The frozen area presents uniform destruction throughout the lesion, even at the periphery.

C. Clinical Application for Hemorrhoids

Since 1969, when Lewis et al (40) reported on the subject of cryohemorrhoidectomy, a number of surgeons have practiced the cryogenic technique for hemorrhoidal disease with gratifying results. We have reported the early results of 50 cases and have found cryohemorrhoidectomy to be a useful method for the treatment of hemorrhoids (67). Since our report, we have performed over 200

Fig. 3. Electron microscopic view. Profound histologic changes and diffuse necrosis are seen two hours after freezing. Irreversible changes have occurred after three days.

Fig. 4. Schematic summary of cryodestructive mechanisms. Combination of mechanical insult, chemical derangement and vascular stagnation.

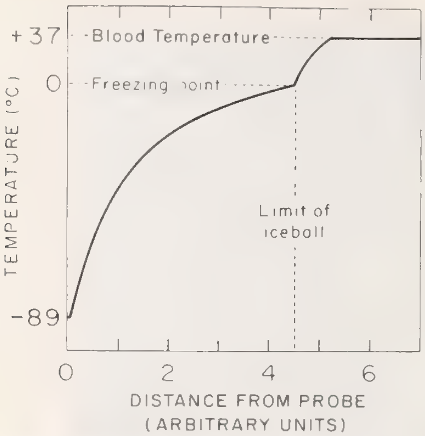

FIG. 6. Idealized diagram of temperature profile through the iceball. Lowest temperature (−89°C) at the tip of the probe and 0°C at the periphery of the iceball.

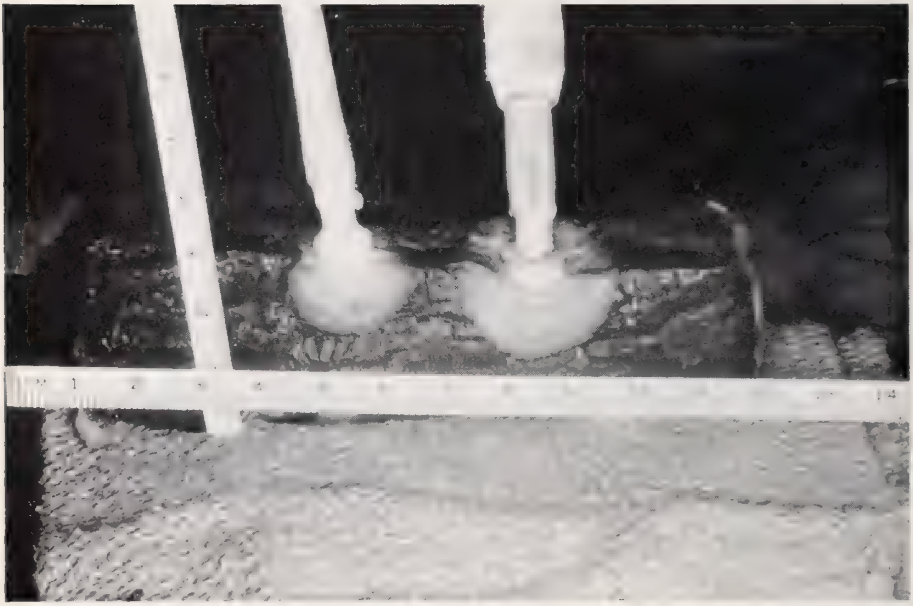

FIG. 7. The pattern of iceball formation: The spread of the iceball is almost equal in its lateral and vertical extension.

cases. Herein we shall analyze cryosurgery, citing both its advantages and disadvantages.

Clinical Material: Cryotechnique was utilized on 200 patients, 109 men and 91 women, ranging in age from 19 to 85 (an average age of 48). Twenty-eight patients had first degree hemorrhoids, 90 had second-degree, 50 third-degree, and 15 had combined hemorrhoids. The remaining 17 patients had external hemorrhoids and experienced no preoperative bleeding (Fig. 9). All patients had preliminary proctoscopy and sigmoidoscopy, and barium enema examination where indicated. Most patients were in good health, except for a few patients

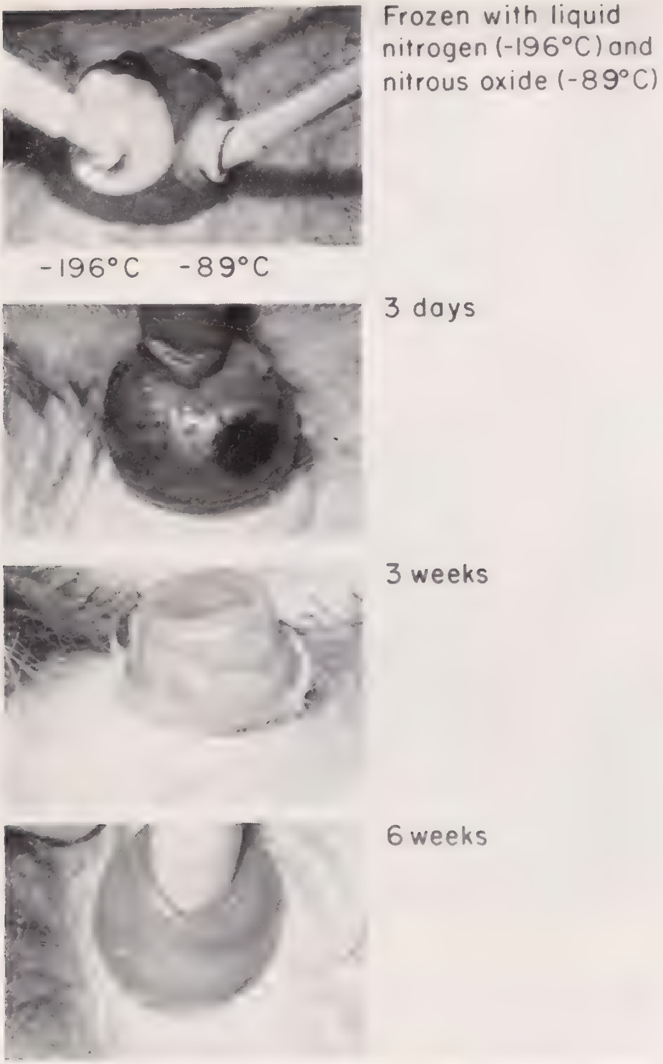
Frozen with liquid nitrogen (-196°C) and nitrous oxide (-89°C)
-196°C
-89°C
3 days
3 weeks
6 weeks

FIG. 8. The clinical course of the cryolesion of the dog colostomy stoma. The cold-insulted area undergoes necrosis and heals with a smooth scar.

who had the following additional conditions: 6 patients had experienced previous surgical hemorrhoidectomy; 3 patients had advanced hepatitis with massive ascites; 1 had multiple sclerosis and needed a wheelchair; 1 underwent double valve replacement; 1 was a paraplegic; 1 was mentally retarded; 1 was bedridden due to old age and pulmonary condition; 4 had severe heart disease; 2 had diabetes mellitus; 1 was blind; 3 had shock from hemorrhoidal bleeding; 1 had liver metastases secondary to rectal carcinoid; 3 had gastric ulcers; 2 had renal failure. The main presenting symptoms were bleeding (84 patients), pain and bleeding (60 patients), pain only (37 patients), discomfort and itching (19 patients).

Indications: All types of hemorrhoids were treated with this technique except

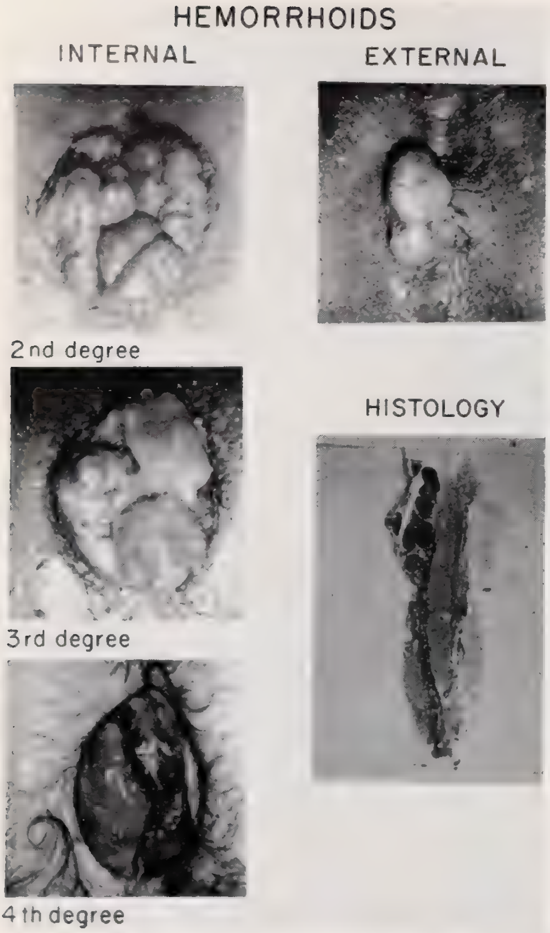

FIG. 9. Various types of hemorrhoids. The prolapsing internal hemorrhoids accompanies the engorgement of the external component which is different from true external hemorrhoids.

those with associated anal infection, fistula, abscess, fissure, gangrene (fourth-degree hemorrhoids), and marked anal stenosis. However, we observed some difficulty in performing procedures on those who had diffusely engorged external hemorrhoids with irregular skin tags. It is quite uncomfortable for the patient to have this procedure because the postoperative foul odor from necrotic tissues is quite unpleasant for him, particularly in warm weather. Difficulty is also encountered when dealing with very nervous or uncooperative patients, some of whom can hardly withstand the pressure or pain of a simple anoscope. Such patients require local infiltration of Xylocaine® and experience a very uncomfortable, even painful, postoperative course. So far we have conducted all our cases as ambulatory procedures, but those who have diffuse external hemorrhoids may benefit from surgical procedures while those who have a low pain threshold will probably do better with general anesthesia.

Preparation: On the morning of the operation the patient should have a complete bowel movement. An enema or laxative to evacuate stool is not necessary.

He can eat his usual breakfast or lunch, depending on the operating time. One-half hour before the scheduled procedure the patient reports to the Ambulatory Unit. Premedication is administered to the patient, an oral table of Percodan® and, if indicated, 5–10 mg of oral Valium®. In our early experience, premedication was 10 mg of Valium or 50 mg of Demerol, I.M.®, but we have found injection not only unpleasant to the patient but unnecessary. Tranquilizers or analgesics are not given routinely but selectively when the patient's emotional condition and or the contemplated procedure warrants it. Medication is often required for the external hemorrhoid, or protuding papilla, which is innervated by the somatic nerve, but may be unnecessary for internal hemorrhoids. The patient is then escorted to the operating room and placed on the table in the jack-knife position. Five percent Xylocaine ointment is rubbed into the anal canal. After five to ten minutes the buttocks are spread with adhesive tape and the anal verge is carefully inspected to confirm the hemorrhoids as the patient bears down. The validity of Xylocaine ointment cannot be overemphasized, but its effect varies in many cases.

Cryoinstruments: Two types of delivery systems are used: nitrous oxide and liquid nitrogen. The choice of instruments is largely dependent on the individual surgeon's preference, so it is difficult to reach a conclusion on the most suitable unit. There is some difference from one maker to another or one system to another. We have tried a number of models both in liquid nitrogen and nitrous oxide. Most hemorrhoids were effectively treated with N_2O (−89°). Various types of cryoprobes have been designed with the cooperation of Frigitronics, Inc., and the appropriate model will be selected in the near future. The CT-73 by Frigitronics, Inc., is presently being used. The nitrous oxide results in the lowest temperature of −89° C, while liquid nitrogen reaches −196° C, with better destructive power than the former. However, liquid nitrogen produces a cloud stream which obscures the operative field and adhesiveness to the target organ is not stable. Therefore it is quite difficult to control selective destruction through the anoscope. Other practical points of view are the obtainability of material. The nitrous oxide cylinder is universal and can be obtained easily, while liquid nitrogen is not stocked in every hospital and is easily vaporized, so that a storage tank is necessary. With a clear understanding of the pathophysiology of the cryodestructive mechanism, most hemorrhoids or allied tumors can be eradicated readily with nitrous oxide units.

Method: The principle of cryohemorrhoidectomy is to completely eradicate the hemorrhoids, either external or internal, by applying profound cold temperature ranging from −89° C to −196° C. As indicated in the previous chapter, the frozen area undergoes necrosis and heals with a smooth scar within three to six weeks following insult. In general, the large vascular and squamous tissues are relatively resistant to cold injuries. Thus the method is varied to suit the characteristics of the tissues. It can be divided into three methods: 1) Direct freezing; 2) Ligation followed by freezing; 3) Freezing and ligation.

External hemorrhoids and first-degree or early second-degree hemorrhoids are treated with direct freezing (Fig. 10). The probing time is between three and five minutes with the nitrous-oxide unit. However, the cylinder pressure should

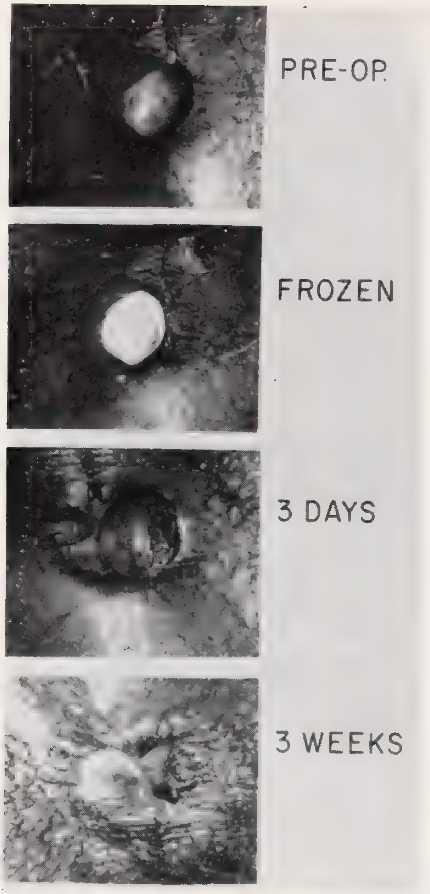

Fig. 10. Direct freezing of external hemorrhoids and its clinical course (from C. Oh and D. Dreiling, Mount Sinai J Med 41:658, 1974).

be maintained above 700 pounds. If the pressure drops below this level, freezing time should be prolonged. The squamous epithelium and highly vascular lesions are relatively cryoresistant and repeated freezing is advisable. If one does not have a clear idea of the destructive limits or powers, incomplete freezing is frequently seen. Every case must be adjusted to the lesion or location. Rarely is the sphincter muscle destroyed with this technique. The depth of freezing is guided by the lateral extension of the ice-ball, since the vertical extension of the ice-crystal is almost equal to the lateral extension. Once the ideal point is reached, both in the size of the ice-ball and in application time, the gas flow should be terminated. When refreezing is required, the surgeon should wait a few minutes until the ice-ball thaws completely, then apply the probe again. This second freezing period is usually less than the first; in most instances it takes two or three minutes.

Ligation followed by freezing: Large prolapsed hemorrhoids, because of their high vascularity and broad dimension, are less effectively destroyed by simple freezing. However, when circulation is blocked by ligation, the resulting tuft is

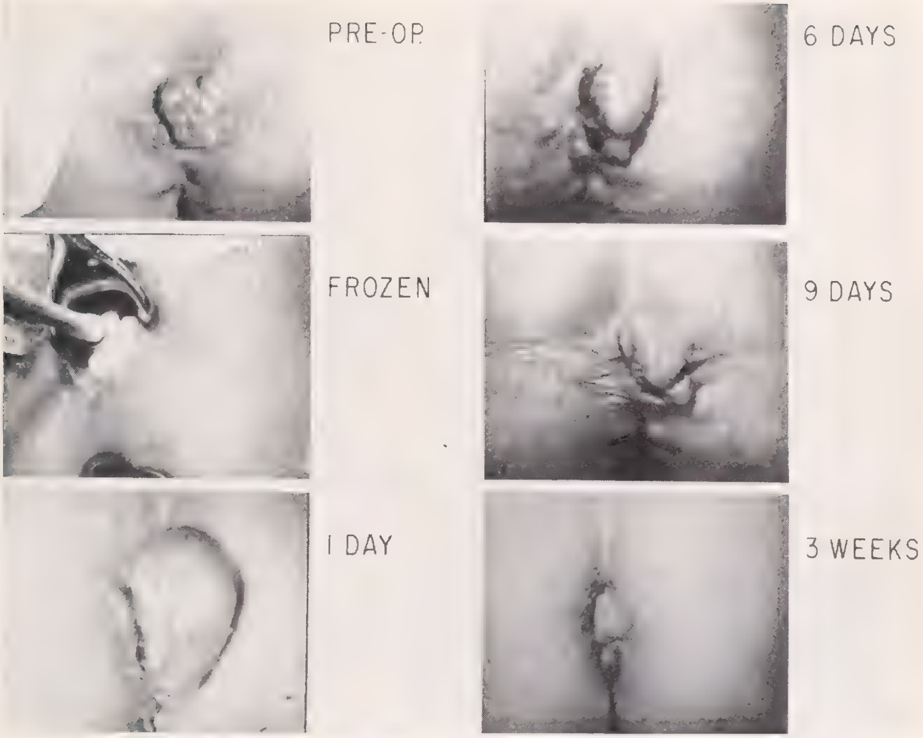

FIG. 11. Direct freezing the prolapsed internal hemorrhoid. Note the marked edema of the lesion (from C. Oh and D. Dreiling, Mount Sinai J Med 41:658, 1974).

avascular and can be frozen readily and is covered by the ice-ball more widely. Ligation not only facilitates freezing but reduces protruding hemorrhoids, avoiding excessive anal discharge and strangulation. If one freezes the prolapsed internal hemorrhoids without reduction, the postoperative course will be complicated with profuse discharge and edema (Fig. 11). This complication can be prevented by reducing the hemorrhoids with ligation (Figs. 12 and 13). Simply ligated hemorrhoids undergo necrosis and dislodge in a week or ten days. Most surgeons treat them one at a time and repeat at a three- to four-week interval, because ligation of hemorrhoids results in considerable pain and discomfort. Cryosurgery allows a smoother and shorter postoperative course and can be completed in one procedure with less discomfort. Also, in the event of incomplete ligation in patients with fibrosis due to previous repeated injections of sclerosing agents, cryodestruction can aid in its complete eradication. The disadvantage of this method is excessive bleeding from the prematurely dislodged hemorrhoidal plexus with a formation of chronic ulcer. However, this complication is minimized by freezing the tuft beyond the ligation O-ring which causes vascular stasis at the base. We have recently added a small incision at the top of the ligated tuft in order to create the vent for leaking fluids freely as they accumulate in the tuft. This maneuver makes possible an even smoother course for the patient as

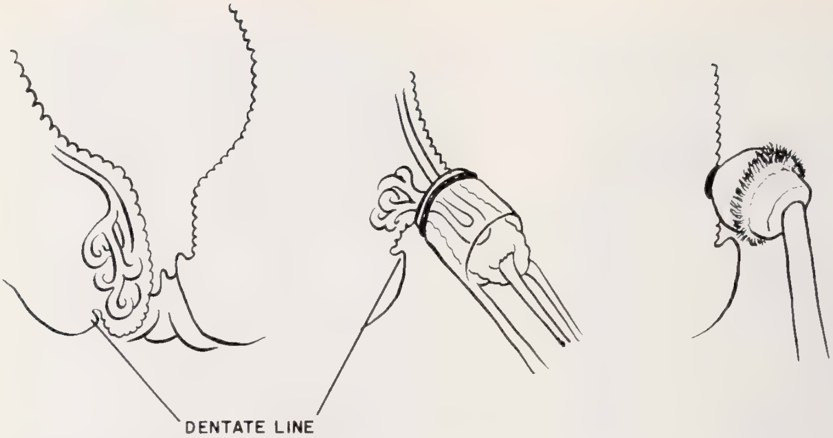
DENTATE LINE

Fig. 12. The schematic drawing of ligation demonstrates that the prolapsed hemorrhoid is reduced into the anal canal.

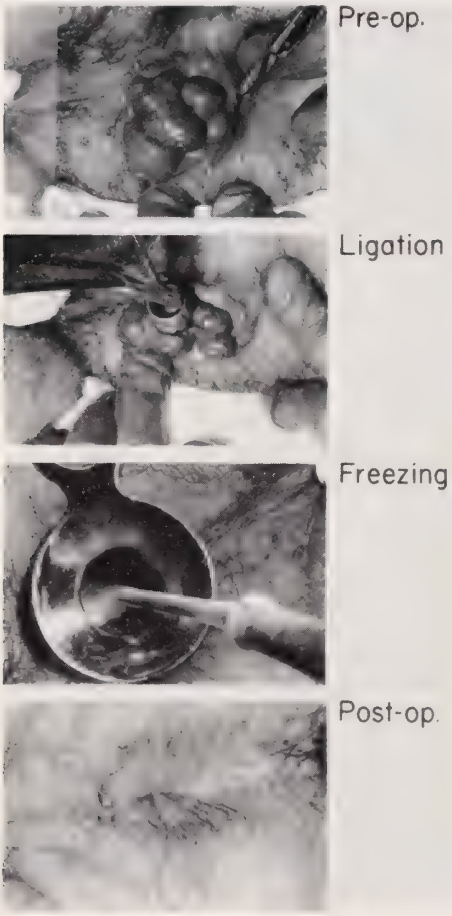
Pre-op.
Ligation
Freezing
Post-op.

Fig. 13. Prolapsed hemorrhoids were reduced with ligations and freezing of the tufts. Note the disappearance of external engorgement following completion of the procedure.

irritation of the anal mucosa is far less than in the suddenly enlarged frozen tuft. Before we applied the ligation technique for the second- or third-degree hemorrhoids, we had had a very uncomfortable experience in that the hemorrhoids were prolapsed during defecation and became irreducible because of massive swelling of the frozen hemorrhoids. It appeared as fourth-degree hemorrhoids, and the postoperative course was dreadful. However, with ligation, the hemorrhoids were kept in the anal canal during defecation and necrosis was completed within two to four days.

Freezing and ligation: It is interesting that after the first cycle of freezing and thawing the anal skin is so insensitive to pain that ligation of the anal papilloma or large skin tags is possible. Such a distinctive feature is useful in the treatment of a relatively cryoresistant epithelioma. When the cryoprobe is applied to the neck of the papilloma some patients complain of pain or severe burning, in which case an injection of Xylocaine at the base of the stalk and continuous freezing is helpful. After complete thawing, the neck is ligated and the redundant polyp can be excised if it is too excessive, the base refrozen just beyond the ligation. This method results in less postoperative pain than does a simple excision using local anesthesia. An alternative method is to freeze the whole papilloma or tags two or three times, then wait a week. If the target tissue is partially destroyed, then one can ligate the base without further freezing or anesthesia (Fig. 14). Usually the frozen tissue undergoes complete necrosis by the third or fourth day.

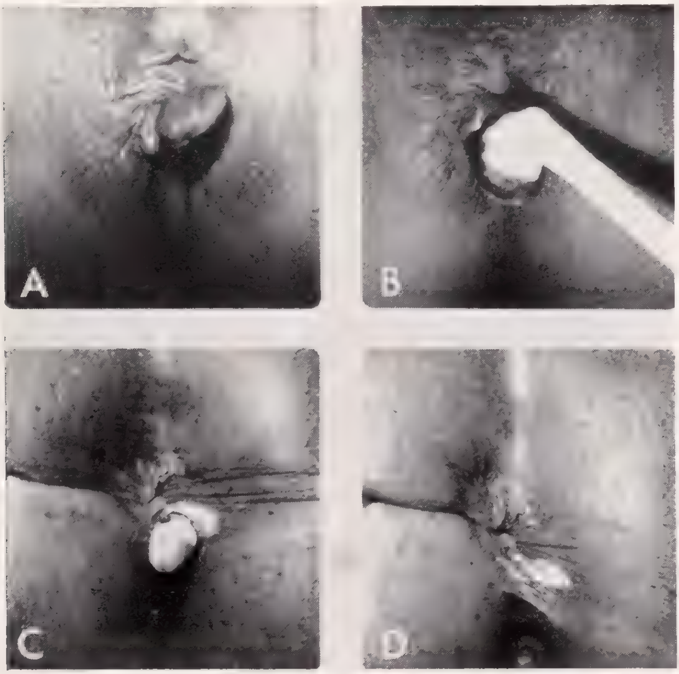

FIG. 14. Clinical course of cryosurgery for anal papillomas: a) Prolapsed papilloma; b) Freezing the papilloma; c) Pedicle of papilloma is ligated at three weeks post-freezing because of intact pedicle; d) Two weeks following ligation (from C. Oh and D. Dreiling, Mount Sinai J Med 41:658, 1974).

In analyzing the first 200 cases, 70 cases were treated with direct freezing; 124 with ligation and freezing; and 6 with freezing and ligation. Among the 124 cases with ligation and freezing, 80 cases were treated with one ligation, 33 cases with two ligations, 9 cases with three ligations, and 2 cases with four ligations.

Postoperative Care: Upon completion of the procedure the patients were returned to the Ambulatory Care Unit, where they remained for anywhere from a few minutes to a few hours, depending on their postoperative condition. Patients who had undergone external freezing usually complained of burning or pain for about a half-hour, but for the others the postoperative course was relatively symptom-free, except for discharge and discomfort for approximately three weeks. Patients who had internal hemorrhoidectomy complained of urgency of bowel movement for the first few days, but few experienced anal pain or discharge. Tylenol®, Valium, and a laxative were routinely prescribed for patients. Occasionally, a stronger analgesic, such as Percodan, was necessary. At other times a local anesthetic agent (Xylocaine suppository) was helpful for soothing anal irritation. Since the anal canal is narrowed as a result of swelling, administration of laxatives is advisable in the early postoperative period. But this may prove harmful if diarrhea or frequent bowel movements are present. The most effective method of controlling anal discomfort is by administering two- or three-minute Sitz baths as frequently as possible and applying Noxzema® cream around the anal verge. It is advisable to follow the patient closely in order to evaluate the postoperative course. Once that course is observed the office visits can be adjusted accordingly. It has been our experience that, if possible, all patients should be seen one week after surgery, at which time the anal condition is checked by inspection or digital examination. One should avoid instrumentation because the friable raw surface may be readily damaged by trauma. If the patient's condition is satisfactory, his next visit can be scheduled for six to eight weeks hence, at which time the anal canal should be inspected through the scope.

Most wounds healed well, except for a few which presented with granulation tissue and required cauterization with silver nitrate. All patients were asked to report between six months and one year after surgery for further followup.

Results: All patients were followed for a three- to 24-month period, during which time no anal incontinence or stricture was found. Wounds were well healed within three to six weeks with little scar formation. Pain was minimal, and most patients needed no more than a mild analgesic such as Tylenol. Approximately one-third of the patients were symptom-free, while the other two-thirds complained of mild to moderate discomfort or pain for a few days (Table II). An analysis of the latter group follows. Sixteen patients experienced pain for a few days and required Demerol or Percodan. Most of them had external hemorrhoids, or their hemorrhoids were prolapsed following surgery. Seventy-one patients experienced mild discomfort but required no medication except for laxatives. Forty-two patients had moderate discomfort requiring Tylenol and or Valium. Postoperatively, most patients returned to work sooner than with the standard surgical hemorrhoidectomy. The period of disability was 1 day in 57 patients, 3 days in 44 patients, 5 days in 39, 7 days in 35, and 14 days in 25 (average of 5

TABLE II

Immediate Postoperative Results

	No. of patients	% of patients
Pain	16	8.0
Discomfort		
Minimal	71	35.5
Moderate	42	21.0
Comfortable	57	28.5
Bleeding		
Mild	5	2.5
Severe	3	1.5
Urinary difficulties	6	3.0
Total	200	100

days). Most self-employed or employer patients returned to work earlier than most employees. The internal hemorrhoidectomized patients returned to work sooner than those who had external or combined hemorrhoidectomy. As in the standard surgical procedures, there were a number of complications. The most serious complication was significant hemorrhaging, which occurred in 3 patients. The first patient was an 82-year-old man who bled on the eighth postoperative day and was admitted to a local hospital where the bleeding stopped spontaneously within 24 hours. The patient required two units of blood. The second case was that of a 72-year-old man who bled on the seventh postoperative day and required two liters of Ringer's lactate. The bleeding stopped without surgical intervention. The third case was a 28-year-old physician (man) who encountered unusual bleeding during the procedure from the torn anal mucosa, which was controlled with manual pressure. However, two hours later, the patient evacuated a fair amount of bloody stool at home. On admission, diffuse oozing was noted at the area of the mucosal tear at the time of surgery. Bleeders were suture-ligated under deep sedation. The hematologic work-up revealed no abnormality, but the patient had a similar episode previously following extraction of teeth. Five patients claimed to have bloody stool between the third and eighth post-operative days but failed to demonstrate any significant bleeding, only minor oozing from the denuded hemorrhoidal bed. Other complications included urinary difficulty in 6 cases, but this was managed without catheterization. Fissure developed in 2 cases without much pain or bleeding; 5 patients complained of burning or tingling sensations following defecation; 3 cases observed spotting of blood once or twice six weeks postoperatively; 54 cases had anal tags, which were mostly seen in the third-degree hemorrhoidal group preoperatively; 5 patients experienced irreducible prolapsed hemorrhoids during the first defecation. This occurred in the patients who had prolapsed hemorrhoids preoperatively because of the swollen hemorrhoids prolapsing during defecation and became irreducible as a result of edema. However, this was prevented in subsequent cases by ligation of the prolapsed portion of the hemorrhoid, thus enabling the edematous hemorrhoidal tuft to remain in the anal canal during defecation. Twelve cases demonstrated clinically visible hemorrhoids at or near a previous hemorrhoidectomized site. Five of these patients required re-operation. Most were warned that they might require repeated procedures because of a multiple, circular type of prolapsed hemorrhoids. It should be noted that all of these patients underwent repeated procedures and did not hesitate to have them done again, as opposed to those patients who were reluctant to repeat a surgical procedure.

All but 19 patients were satisfied with this procedure. Of this group, 12 had recurrence, 5 experienced burning or tingling sensations, and 2 developed fissures.

Comment: Hemorrhoids have been treated surgically since antiquity. However, postoperative pain has been so severe that various other methods have been devised, but with less effective results. There can be no doubt that hemorrhoidal mass can best be eradicated by excision despite the drawback of unbearable postoperative pain which is caused by exposed nerve endings of the wound, and aggravated by local inflammation and sphincteric spasms. These causes can be largely eliminated by destroying the exposed nerve endings and facing the raw surface with insensitive granulation tissue which is resistant to the infection. This criteria has been met in cryosurgery because the nerves at the wound borderline are destroyed by freezing and the underlying wounds are covered with a biological dressing of cold-insulted tissues which undergoes necrosis and separates from underlying tissue in a few days. When the necrotic tissue sloughs off, the raw surface is covered with insensitive and infection-resistant granulation tissue. Hence the postcryosurgical course is relatively painless compared with that of surgical excision.

However, many factors are involved in the accuracy of tissue destruction with this method: size, temperature and adhesiveness of the probe; tissue temperature, conductivity, density and osmolality; and duration of freezing (73). In order to precisely destroy the target tissue, the surgeon must have a clear visual field and must accurately gauge the duration of probe-application according to the character of the tissue and he must closely watch the extent of the newly formed ice-ball.

In the past, cryosurgery has been used mainly in two ways: direct freezing, and ligation with freezing. Lewis et al (40) and William et al (65) froze hemorrhoids directly while Barron (66), Rudd (28) and Fleming (74) ligated the internal hemorrhoids and then froze the tuft. They found that once ligated, the internal hemorrhoids rarely required treatment of external hemorrhoids or tags. Contrary to this, Detrano (64) practiced a method of ligation with freezing for the internal hemorrhoids and then froze the external hemorrhoids separately at the same time.

It is commonly found that patients who have prolapsed hemorrhoids often also have redundant corrugated anal skin in the corresponding area, mainly the left lateral or right posterior and anterior, particularly the right anterior in females. This is probably due to loosened submucosal attachments at the hemorrhoid-bearing area which become elongated and stretch anal skin as the internal hemorrhoids protrude during strain. Therefore, once the internal hemorrhoids are ligated, the corresponding area of corrugated redundant skin usually disappears as it withdraws into the anal canal (Fig. 13). However, excessively elongated, long-standing anal tags may remain at the anal verge but the symptoms which were present properatively usually improve following treatment of the internal hemorrhoids. Hence routine freezing of external skin tags or hemorrhoids is not advisable. This view is shared with others who propose ligation techniques such as Rudd (28), Barron (66) and Salvati (29). Addition of the freezing technique to ligation will shorten and ease the postoperative course, enabling the surgeon to eradicate all hemorrhoids at once and effectively destroy all of them even if the ligation itself is incomplete. Ligation also plays an important role in the treatment of prolapsed hemorrhoids by preventing a recurrence of prolapse during the immediate postoperative defecation.

Since most hemorrhoids are internal, cryotechnique is aptly suited because there is little if any postoperative discharge and malodor. For external hemorrhoids, however, standard surgical postoperative pain must be weighed against the unpleasant postcryosurgical odor when deciding which corrective method should be used.

The fact that there are numerous methods of treatment proves that none has achieved the ideal. The addition of this new method in the armamentarium of surgeons should be evaluated critically and its validity judged by accumulated data. However, at this stage, it is fair to say that, if one understands clearly the pathophysiology of cryosurgery and uses meticulous technique for hemorrhoid repair the results are gratifying both to patient and surgeon. We are convinced that cryosurgery is much more appealing to the patient than the standard surgical technique. A comparative review demonstrates that the cryosurgical method is superior to that of surgical procedure in regard to postoperative pain and disability but the recurrence rate is rather high with this technique (Table 3). Six of our patients had previous surgical hemorrhoidectomy and underwent cryosurgery for recurrent symptoms. All of them expressed a preference for this pro-

TABLE III

*Comparison of the Results of Hemorrhoidectomy**

Method:	Surgical excision	Cryosurgery	
Author: No. of cases:		Lewis (1972) 50	Oh (1975) 200
Pain (%)	33–90	4	8
Hospital stay (days)	3–8	0	0
Disability (days)	14–30	1	5
Urinary retention (%)	0.5–32	0	0
Skin tags (%)	30–34	4	27
Fissure (%)	0.5	0	1
Stenosis (%)	3–9	0	0
Recurrence (%)	1–3	2	6
Minor incontinence (%)	3	0	0
Bleeding (%)	3–4	8	4†

* From references 1, 6, 62 and 67.

† Three patients: hospitalized.

cedure. Five patients had residual hemorrhoids and had to undergo cryosurgery for a second time, and none hesitated to have the procedure repeated, as opposed to repeated surgical excision.

Continuous, critical and meticulous exploitation of this method may greatly aid those with hemorrhoidal disease in the near future.

Acknowledgment

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Carcinoma of the Breast Occurring in a Husband and Wife: A Brief Communication

BERNARD BRUCE WETCHLER, M.D. AND BARRY SIMON, M.D.

The occurrence of breast carcinoma in a husband and wife during a two year interval has not been previously reported. The two case reports are therefore presented.

Case Report

The wife was examined July 1972 for a lesion in her left breast. The lesion was initially noticed by the patient three weeks previously. She was 61 years of age with a relatively normal medical history. She had two pregnancies with two live births and voluntarily did not breast feed either child. Her last menstrual period was in 1962. There is no history of breast carcinoma in her family.

Physical examination revealed a three and a half centimeter lesion in the upper outer quadrant of the right breast. The lesion was in the two o'clock axis near the aureola. It was nontender, not adherent and irregular in outline. There was an absence of axillary or supraclavicular nodes. The left breast was normal. Preoperatively the patient was tentatively entered as a Stage I carcinoma in the National Surgical Adjuvant Breast Protocol.

On August 4, 1972, according to her category in the protocol, a right simple mastectomy was performed followed by postoperative radiotherapy. The pathology report was infiltrating mammary ductal carcinoma. In August 1974, she was alive and well with no evidence of any recurrence.

Her husband, to whom she is married 23 years, was examined July 1974. For periods of a few days every three months he noted a bloody discharge on his undershirt opposite the right nipple. The onset coincided with the date of his wife's mastectomy. He is 60 years old with a negative medical history. He is a retired mail carrier who carried his mail bag on his left shoulder. There is no history of breast cancer in his family.

Physical examination revealed a normal right nipple and breast. No lesion was palpable with an inability to produce the bloody discharge on compressing the nipple. There were no palpable axillary or supraclavicular lymph nodes. The left breast was normal.

On July 26, 1974, an excisional biopsy was performed of the breast tissue beneath the right areolar. Frozen section report was malignant and a right radical mastectomy was performed. The paraffin pathologic diagnosis was intraductal carcinoma.

Comment

A survey of the literature has failed to detect a previous report of carcinoma of the breast occurring in a husband and wife. The specific incidence of carcinoma of the breast in females is 61.9 cases per 100,000 population while in males it is 0.58 cases per 100,000 population. The possibility of it occurring in a husband and wife is therefore remote.

This case report is also unusual in several aspects. The male's bloody nipple discharge commenced at the time of his wife's mastectomy and she noted her

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lesion for only three weeks. Both lesions occurred in the right breast and the patients were of almost identical age. The pathology of both carcinomas was ductal and neither patient demonstrated any nodal involvement or distant metastasis.

Summary

A case report is presented of breast carcinoma occurring in a husband and wife. Numerous similarities are noted. The clinical significance of this occurrence is not evident.

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Thyroid Carcinoma Presenting As Epidural Metastasis with Spinal Cord Compression

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Thyroid carcinoma initially manifesting as metastases to the epidural space with spinal cord compression is rare. Although thyroid carcinoma infrequently metastasizes to the spinal epidural space (1–4), it usually does so as a late event when the primary diagnosis has already been established (4). Thyroid symptomatology and/or evidence of other thyroidal metastases have already appeared. For thyroid carcinoma to present as epidural metastases and spinal cord compression without other symptomatic evidence of primary or metastatic disease is most rare. Review of the literature reveals only six previous such cases (5, 6). In these, the combination of early decompressive laminectomy followed by thyroidectomy and radioiodine therapy proved to be therapeutically effective (5, 6).

Case Reports

Case 1: A 57-year-old white male was hospitalized at the Veterans Administration Hospital on August 15, 1973 with an eight-week history of aching, nonradiating pain over the upper thoracic spine and a ten-day history of rapidly progressive numbness and weakness of both lower extremities. The pain was worse at night and aggravated by movement. There was no associated urinary incontinence or retention. The patient denied weight loss, tremulousness, palpitation, excessive sweating, nervousness, somnolence, muscle cramps, hair or skin changes, hoarseness, or cold intolerance. He had previously been in good health and his family history was not remarkable.

Examination: The thyroid gland was enlarged and a palpable, firm nodule was present in the right lobe. There was no regional lymphadenopathy. Spinous process tenderness from T_4 to T_7 was noted. Rectal sphincter tone was good. The patient had a grade III weakness of all muscle groups of both lower extremities and a loss of pinprick sensation bilaterally below T_7. Patellar and Achilles reflexes were 3+ and symmetrical. Bilateral Babinski's were present. X-rays revealed erosion of the pedicles at the T_5 and T_6 levels. Emergency pantopaque myelography demonstrated a complete block at T_5 secondary to an extradural lesion.

Operation: On the evening of admission a decompressive laminectomy from T_5 through T_7 was performed, with the removal of an epidural tumor. The mass had invaded the T_5 and T_6 lamina and had extended into the left paravertebral region. At the end of the procedure pulsation of the dural sac was noted.

Pathologic Examination: The specimen consisted of several small pieces of greyish-brown tissue mixed with bony fragments, measuring 8 cc in aggregate. Microscopic examination revealed the tumor to be composed of sheets and trabeculae of monomorphic cells lacking significant atypism or mitotic figures. Vascularization was prominent and the "endocrine" pattern of the tumor was evident (Fig. 1A). In places, characteristic thyroid follicles were seen, mostly empty, but sometimes partially filled with colloid (Fig. 1B).

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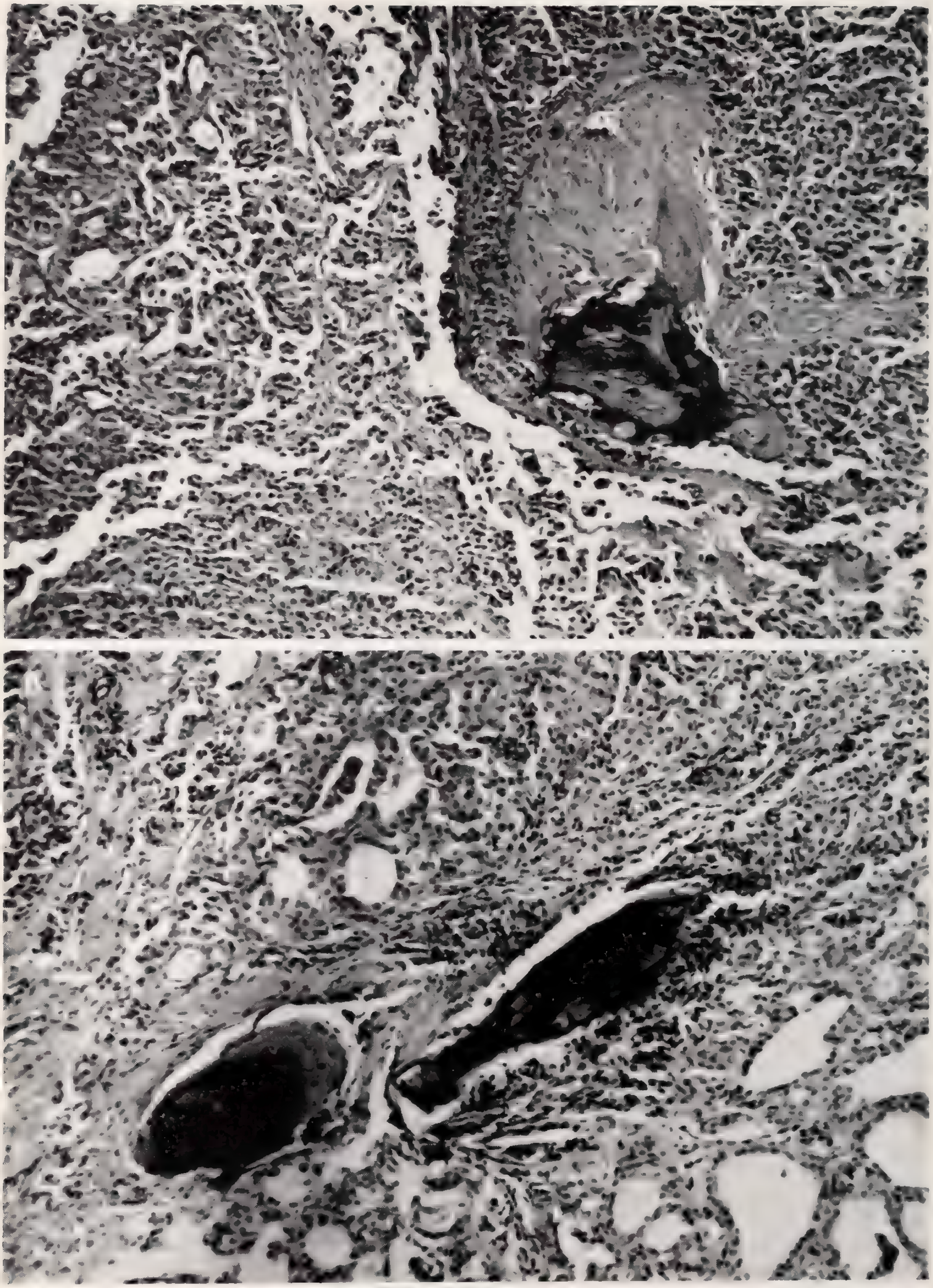

FIG. 1. A: Metastatic thyroid carcinoma infiltrating epidural space and lamina of T_5 and T_6 vertebrae (Case 1). Note follicle formation (left upper) and a bony spicule (right field) (H&E × 100).

FIG. 1. B: Typical thyroid follicles predominate in this field (H&E × 100).

Postoperative course: Twenty-four hours after surgery, the patient was able to lift his lower extremities against resistance and on the third postoperative day he was walking with assistance. On the seventh day an I^{131} tracer test was performed and showed thyroid clearance and 24-hour uptake of radioactive iodine to be at the lower border of the euthyroid range. Two days following this a thyroid and whole body scan were done. This revealed a nonhomogeneous, abnormal pattern of I^{131} accumulation in the right lobe of the thyroid; the left lobe taking up virtually no isotope. There was no accumulation of the isotope elsewhere in the neck, and the body scan disclosed no evidence of functioning thyroidal metastases. PBI determinations were obtained at two and four weeks postoperatively. Both readings were greater than 50 mcg%. Six weeks after surgery the T_3 measurement was 44.6%, and T_4 6.1 mcg%, both within normal limits. A bone survey was negative except for the known thoracic spine involvement. On October 1, 1973, the patient underwent a total thyroidectomy.

Pathologic Examination: The specimen consisted of an enlarged and somewhat nodular thyroid gland, weighing 85 grams and measuring 12 × 7 cm in largest dimension (Fig. 2). The entire left lobe was replaced by a nodular, firm, light grey-tan tumor mass. Within the right lobe there was a well-demarcated, fairly round tumor measuring 4 cm in its largest diameter. Areas of cystic degeneration were noted. Microscopic examination showed the tumor occupying the left lobe to have the typical appearance of follicular thyroid carcinoma (Fig. 3A and B). The right lobe tumor proved to be an adenoma.

Eight weeks postthyroidectomy a radioiodine scan demonstrated uptake over the involved thoracic spine region, which was not present preoperatively. In December 1973, the patient received a radioiodine dose of 100 millicurie. Subsequent scanning revealed continual I^{131} accumulation in the spinal metastases. Presently, the patient is being followed by the Nuclear Medicine service, and further radioiodine therapy for the residual thyroidal metastases in his thoracic spine is being considered. The patient's neurological status has improved. He is ambulatory with good strength in his lower extremities and with minimal sensory deficit.

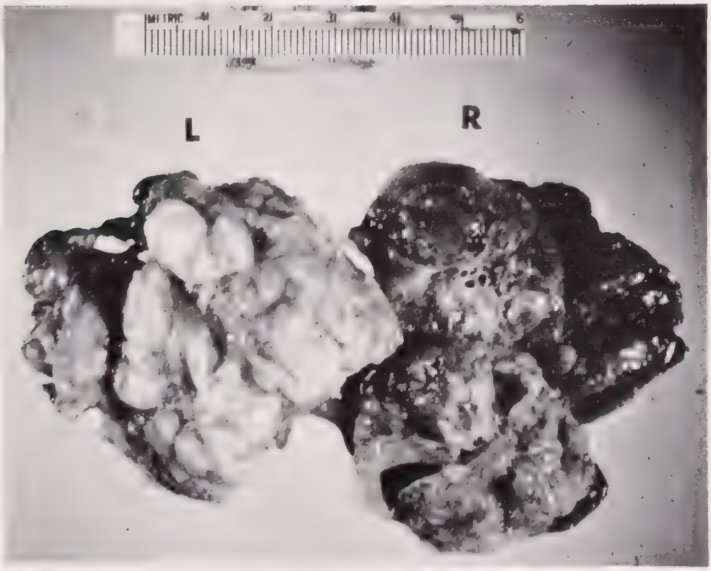

FIG. 2. Bisected thyroid gland (Case 1). The entire left lobe (L) is replaced by fleshy follicular carcinoma. An adenoma with partial cystic degeneration, fibrosis and calcification is evident within the right thyroid lobe (R).

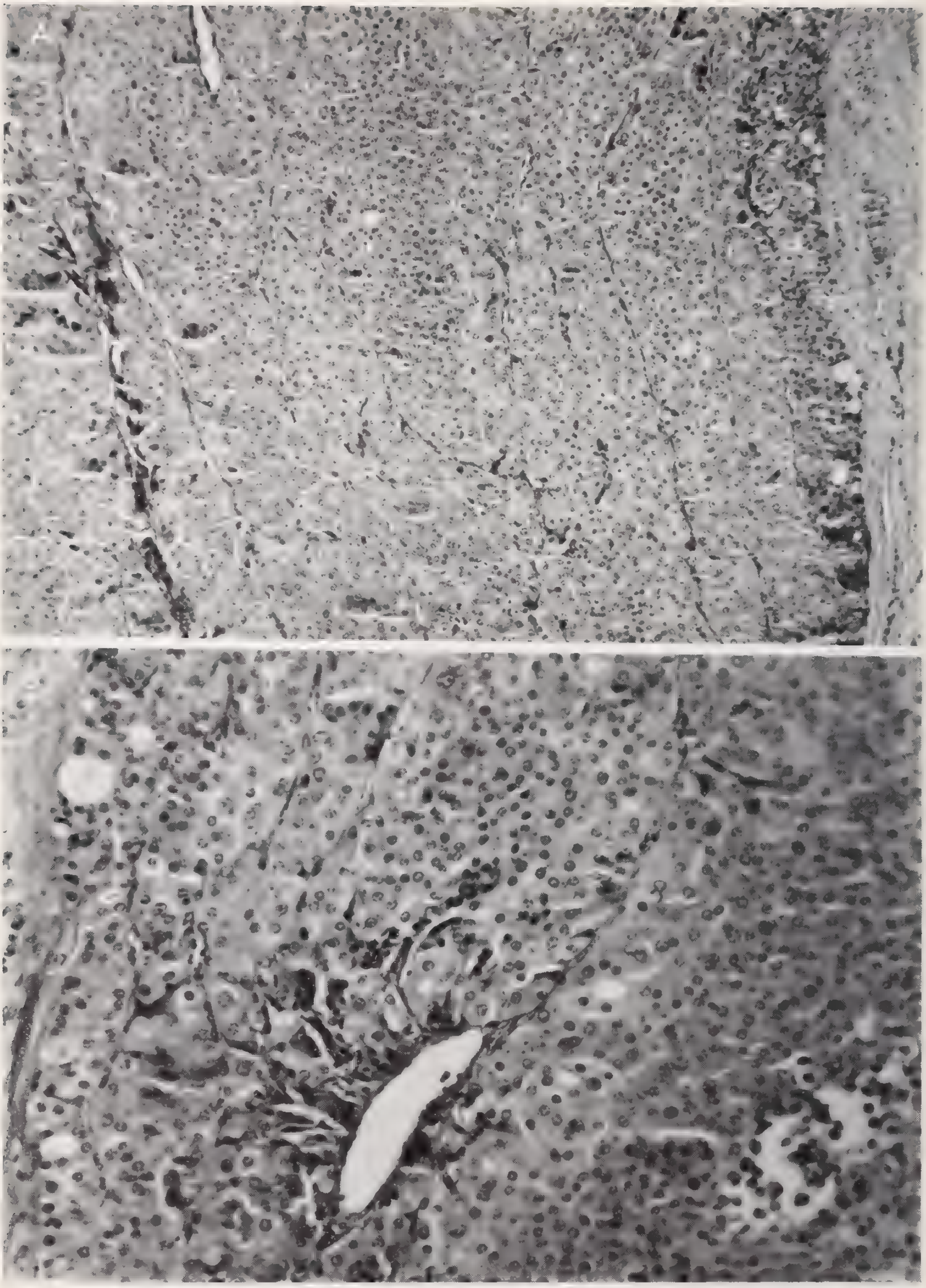

Fig. 3: A: Monotonous sheets of follicular thyroid carcinoma (thyroidectomy specimen, Case 1). Occasional foci of follicular differentiation are to be noted (extreme right) (H&E × 100).

Fig. 3. B: Higher power microphotograph illustrating the cytologic details of the carcinoma cells. Note absence of significant pleomorphism and mitotic figures (H&E × 200).

Case 2: A 56-year-old white male was admitted to the V. A. Hospital in August 1949 with a four-year history of intermittent low back pain radiating down both lower extremities. Six months prior to admission, the patient complained of progressive weakness of both legs. One year prior to admission, a swelling in the upper lumbar region was noted, and a biopsy done in March 1949 revealed metastatic thyroid carcinoma. The patient had no thyroid symptomatology.

Examination: No detectable mass was evident in the neck region. A pulsatile mass, however, overlaid the second lumbar vertebrae. There was general weakness of all muscle groups in the lower extremities, more marked in the quadriceps and tibialis anterior. The patient had diminution of touch and pain and absence of reflexes in both lower limbs. X-rays of the spine demonstrated lytic lesions involving the second lumbar and sixth cervical vertebrae. Radioiodine uptake was found to be normal over the thyroid and present over the involved spinal areas.

Operation. A large dose of radioactive iodine was given to ablate the thyroid, and this was followed by surgical thyroidectomy in September 1949. Three-quarters of the gland was removed, including a nodule in the right lobe which was thought to be the primary site of the tumor.

Pathological Examination: The right lobe and half of the left lobe of the thyroid gland were submitted. A fairly well-circumscribed tumor mass measuring 2 × 3 cm, was seen in the lower pole of the right lobe. It consisted of pale yellowish-pink tissue. The gland was grossly nodular (weight and measurements were not stated) (Fig. 4). Microscopic examination revealed a typical pure follicular carcinoma of thyroid (Fig. 5).

Following the ingestion of radioactive iodine and thyroidectomy, the back pain was markedly reduced. The patient was able to walk with a back and cervical brace by the time of discharge.

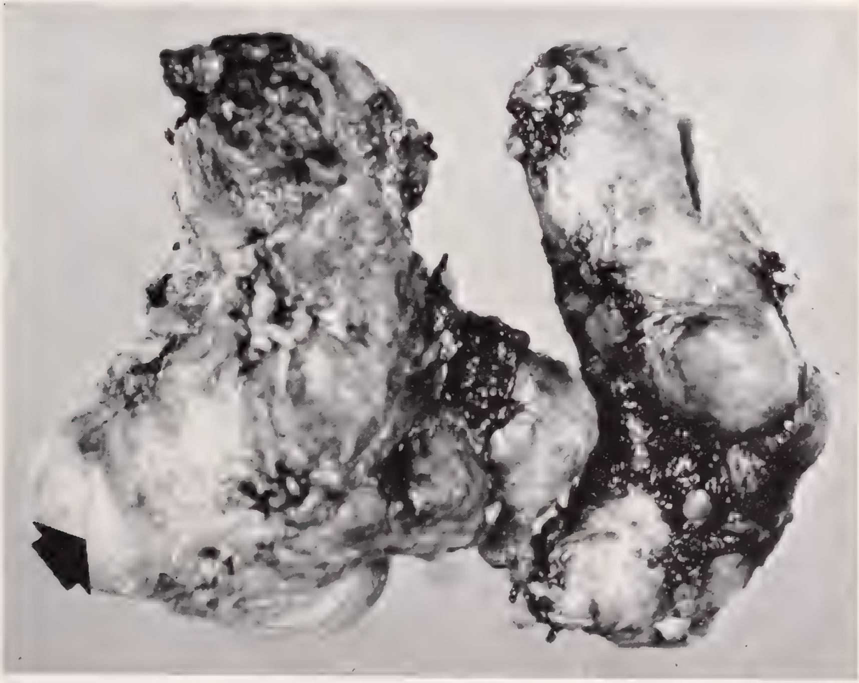

FIG. 4. Thyroidectomy specimen (Case 2). The site of the follicular carcinoma in the right lower lobe is marked with an arrow.

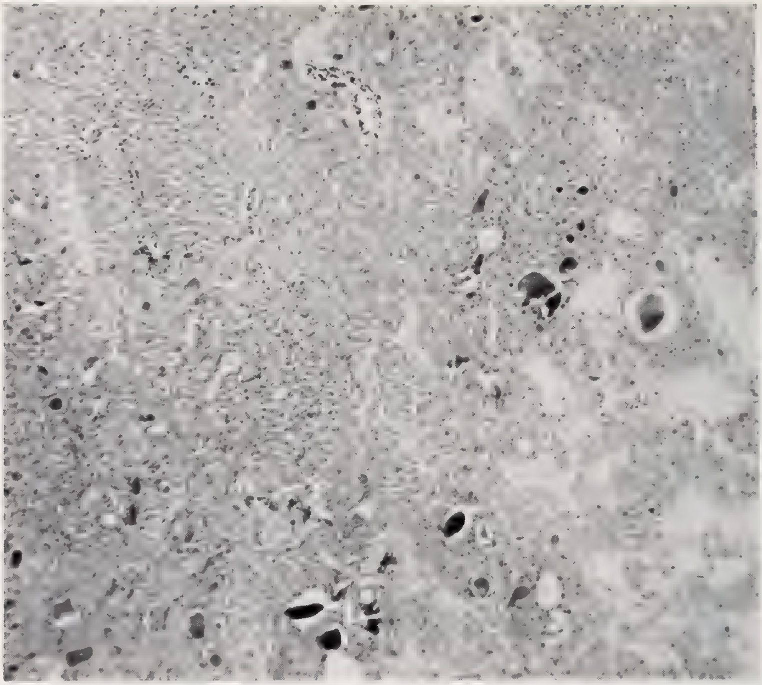

FIG. 5. Representative field of the follicular carcinoma of the thyroid (Case 2) showing sheets of small cells and follicles filled with colloid (H&E × 40).

The patient was readmitted in February 1950 for further radioiodine therapy of his vertebral and epidural metastases. A neurosurgical consultation noted that on this admission the patient was greatly improved, with good strength in both lower extremities. Reflexes were active bilaterally. Minimal sensory deficit was still present. The pulsating mass in the lumbar region was no longer evident. X-rays revealed lytic lesions involving C_6, T_7 and L_2. When compared with the previous films, there appeared to be an increase in the amount of calcification and evidence of trabecular formation. On March 5, 1950, the patient was begun on thiouracil treatment, 1.5 grams daily, in an attempt to make the metastases more amenable to radioiodine therapy. This was discontinued four weeks later when toxic effects on the lymphocytic series and kidneys were noted. Following this, the patient was given a therapeutic dose of radioiodine (148 mc).

The patient was followed by the Nuclear Medicine service for continued evaluation and radioiodine therapy during the subsequent years. He died in 1966 of leukemia without clinical evidence of thyroid metastases. An autopsy was not granted.

Discussion

Despite the presence of distant metastases, the prognosis for some types of thyroid carcinoma is exceptionally good. The most benign and histologically well-differentiated thyroid carcinomas are the papillary and follicular forms which have ten-year survival rates of 90% and 75% respectively from their time of onset (1).

Tumors of the thyroid metastasize frequently, and often metastasis is the first clinical manifestation of a silent primary tumor. Sites of thyroid metastases include lymph nodes, bone, central nervous system, lung, liver, adrenal and kidney (7–11). In a statistical study of 390 patients with carcinoma of the thyroid gland, Hirabayaski and Lindsay (1) found that 42% of the cases had metastasized to the regional lymph nodes at the time of initial surgery for tumor removal, and that another 16% had distant metastases at this time. The incidence of thyroid carcinoma metastasizing to the vertebral column and epidural space is very low (1–4). Barron, Hirano, Araki and Terry (4) reported a study of 127 patients with epidural metastases, only three of which originated from a thyroid neoplasm. Alexander, Davis and Field (2) published a series of 21 cases with metastatic lesions of the vertebral column causing cord compression and only one of these was of thyroid origin. Tumors that more commonly metastasize to the epidural space are carcinoma of the lung, breast, kidney, prostate, and malignant lymphoma (2–4; 6, 12).

Extradural metastatic tumors of the spinal cord are distinguished by their relatively acute onset and rapid progression. The course to maximum neurological deficit is often measured in hours or days (2, 5, 13). Regardless of their location, extramedullary tumors may produce a wide range of symptom complexes with no characteristic pattern. Pain is the most common and outstanding symptom, followed by weakness, paresthesias and bladder disturbances (2, 4, 13). Paraplegia is the usual consequence and is invariably accompanied by loss or impairment of all forms of cutaneous sensation below the level of the lesion. The earlier the treatment is instituted the more complete the recovery is likely to be. In 50 cases of extradural neoplastic lesions treated by Mullan and Evans (3) with decompressive laminectomy and postoperative radiotherapy, 32% had good results; the patients recovered from their neurological deficits and remained symptom free and often gainfully employed for the greater part of the life expectancy of their disease.

The first use of radioisotopes in the treatment of cancer was the use of I^{131} in treating malignancy of the thyroid (14). Although the isotope is biologically and selectively localized in the thyroid, the types of thyroid carcinoma that respond to this therapy are limited to the follicular and papillary forms (14).

Primary thyroid tumors with early metastasis to nodes in the neck are generally treated by total thyroidectomy and local lymph node dissection (1, 3–5). Distant metastases of favorable histologic types are then considered for radioiodine treatment. It is important, however, that prior to radioiodine therapy, normal functional thyroid tissue in the neck be removed since it competes with functional metastases for the circulating radioiodine, leaving little or none to be localized in the metastatic areas. Once the thyroid has been removed, metastases often increase in size and function due to a fall in thyroxine and stimulation by TSH (14). Pochin (15) found that 80% of well-differentiated thyroid metastases took up radioiodine if sufficient time elapsed following thyroid removal. In his study of 104 patients who showed clear radioiodine uptake, one third exhibited their uptake in tumor metastases before or at the time of thyroid removal, and two-thirds obtained radioiodine uptake seven to twenty-four weeks later (15). In our first case, radioiodine uptake was demonstrated eight weeks following thyroidectomy. Pochin (15) found that 50% of his patients so treated showed progressive response to successive doses with an abolition first of clinical evidence and later of any evidence of functional thyroid metastases. An average of six radioiodine doses of 150 millicurie each were given during a mean three-year period; the time required to abolish any evidence of remaining tumor activity. Pochin (15) assumed complete tumor destruction when uptake no longer was detectable at the previous known sites of functional tumor tissue. In some patients (one out of ten in his series) very little regression of the tumor size occurred despite good radioiodine uptake.

Pochin (15) and King and Sharpe (14) noted bone marrow depression with multiple radioiodine doses of 100 150 millicurie. In Pochin's (15) series, radioiodine therapy had to be discontinued in five patients due to the development of an aplastic bone marrow; four of these patients developed leukemia, as did our second patient.

Iodinated compounds, such as myelographic contrast materials, can dilute an administered dose of radioiodine within the body and therefore decrease the uptake of radioisotope by thyroidal tissue and metastases, thus impairing the effectiveness of the radioiodine therapy. In addition iodinated materials may invalidate diagnostic tests of thyroid function involving measurements of iodine, such as protein-bound iodine (PBI), for several years following their intrathecal injection.

Summary

Metastasis to the epidural space from thyroid carcinoma has a favorable prognosis. If detected early at a time when minor and less acute neurological deficit is prevalent, decompressive laminectomy may not be necessary—thyroidectomy followed by radioactive iodine therapy may suffice.

Two cases of thyroid carcinoma initially presenting as spinal cord compression secondary to epidural metastases are reported. The clinical characteristics and findings as well as the therapeutic considerations are discussed.

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Disturbances of Psychosexual Development of Adolescent Girls*

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Abstract

While neither males nor females are irrevocably restricted to a biologically predestined and sharply delimited sex role, basic genetic and biochemical factors tend to be overlooked or assigned a very peripheral role in sex-linked behavior patterns by proponents of "Sexual Liberation." The overlap of social, psychological, and biological factors that influence psychosexual development is exemplified in two paradigmatic psychosomatic disorders frequently encountered among adolescent girls: obesity and anorexia nervosa. The psychodynamic implications of these conditions and their relevance to disorders of psychosexual development in female adolescents are delineated. Brief case illustrations utilizing projective test data are included.

The term "psychosexual" refers to the interplay between biological and psychological factors that influence the development of a balanced and mature personality capable of establishing enduring interpersonal and heterosexual relationships in adulthood. Perhaps one might also coin the term "sociosexual" to describe the interaction between raw biological processes and the manner in which these are shaped and oriented by the social milieu in which they occur. We are beginning to learn a great deal about early sex-typing and the degree to which social roles and self-concepts are molded by parents, teachers, the media, books, and other influencing forces. These serve as carriers for socially approved mandates concerning the desirability of behaviors and attitudes considered appropriate for a given sex. The recent rise of Women's Liberation has called attention to the tradition-sanctioned injustices perpetrated upon women throughout the ages, beginning, according to the Movement's proponents, with the assignment of specific toys and play activities for each sex as a way of indoctrinating the child with a narrow and confining "sexist" conception of itself. In this view, the passivity of the female and the aggressive activity of the male are products of brainwashing that widen the gap between the sexes and encourage discrimination against females upon the assumption that for them anatomy is destiny (Freud's term). Upon these grounds the assumption is made that fortitude is a masculine characteristic and tearfulness a feminine one, that men are strong and women are weak, and that maleness is equated with dominance and femaleness with submissiveness.

These assumptions are being challenged not only, it is claimed, because they create and perpetuate a false picture of femaleness, but because they imprison the male within a sex-stereotyped image of his role that limits his ability to experience love as tenderness.

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As in every movement energized by revolutionary zeal, exaggerations are unavoidable and basic factors may be ignored. There is a tendency to discount the role of anatomic and endocrinologic factors as determiners of sexual differences, which in turn contribute significantly to each sex's social role formation. What has been made more explicit, after clouds of emotionalized rhetoric have been dissipated, is the fact that neither sex is irrevocably confined to a biologically predestined restricted role and that there are available options that, if accepted, can broaden and deepen the humanness of each sex.

Many of the phenomena observable in this age of the so-called "sexual revolution" can then be understood as a conglomeration of adaptive and maladaptive attempts to take advantage of these options and to do so within a context of those excesses that characterize a release process. The dismaying incidence of instant loveless sex among adolescents, the proliferation of pornography and violence, group sex, wife-swapping, unisex apparel, and other manifestations (1) may well represent trial-and-error efforts to achieve a type of relationship between the sexes that will be free of false inhibitions, role-playing that is imposed by a sexist society and which violates the essential humanness of the individual, and the neurotic interactions that plague so many marriages and bring them to the divorce courts.

However, it would be foolhardy and a disservice to one's patients to accept a strict environmentalist conception of psychosexual development. Biology and culture overlap and interact in a complex manner, and many of the disorders of childhood and adolescence can be traced to asynchronies between the two. These can be attributed to deviations from normative developmental tempos, traumatic experiences, unwise or destructive parental management, disruptive fantasies in the child and adolescent that have assumed the cloak of reality, and neurotic or psychotic conditions.

The vicissitudes of psychosexual development as delineated by Freud and corroborated by intensive analysis of thousands of men, women, and children, as well as confirmatory evidence provided by psychologists who assess personality with projective techniques such as the Rorschach, Thematic Apperception Test, human figure drawings, and the like, cannot be ignored if one is to acquire an understanding of disorders. That these tests also reflect changes in the zeitgeist was established by my own research on 1,393 patients who were divided into two groups, separated by a 10-year interval; the first group was administered the Rorschach in 1954 and 1955, and the second in 1965 and 1967. The findings showed that males under 24 projected themselves as feminine and more passive in their orientation, and mother-identified, whereas females assumed a posture of what is considered to be masculine dominance and assertiveness. This was highly significant statistically for the later group when compared with the earlier one. These differences were not significant for the over-40 males and females (2).

Freud's developmental schema postulates an oral, anal, and genital progression, with some overlap to be sure. The oral stage focuses upon the mouth as primary pleasure zone in infancy and Karl Abraham writes that an optimistic attitude toward life is likely if sucking pleasure is marked and undisturbed. If the mother has been abnormally indulgent, there may be a tendency to carefree indifference and inactivity in addition to the optimistic attitude. Such individuals, and they encompass underachievers and dropouts, expect that some kind person, a mother figure, will care for them and that mother's milk will "flow for them eternally." Failure to achieve sucking gratification (and, I may add, body contact with mother) may result later in a demanding social attitude, a tendency to cling to others, impatience, and a dislike of being alone.

The anal stage is related to sphincter control and the imposition upon the child of demands for cleanliness. The pleasurable aspects of excretory processes, erotically as satisfying as the erogenous gratifications of the mouth, as well as all anal-erotic activities are tabooed. Control is rewarded with praise and the accolade of being a "good child," whereas soiling and wetting are perceived by the parent as a form of defiance by a "bad" child who is unworthy of love. The child soon learns that love is won by making a virtue out of necessity, and what was once pleasurable is now reacted to as dirty and disgusting. Such traits as reliability, conscientiousness, and in an over-accentuated form, pedantry, avarice, obstinacy, defiance, and compulsivity derive from this stage.

In the third phase, the phallic, the earlier stages are incorporated in a modified form and is finally and predominantly determinative for personality development. This general genital discharge of all kinds of sexual excitement around the fourth or fifth year of life does not mean that genital erogeneity was absent during the earlier phase, but only that sexual excitement from whatever source becomes more intensified at the genitals and is eventually discharged through a genital pathway. For the boy the fear that he may lose this prized organ as punishment for masturbation or in retaliation for hostile wishes toward the father who is his rival for mother's love precipitates the castration complex (4).

The little girl at first believes that everyone is built as she is. When she learns otherwise, according to psychoanalytic theory, she feels deprived and disadvantaged, develops penis envy, and believes she has lost a penis as punishment for hostile impulses toward the mother. The patent social advantages enjoyed by men in the past undoubtedly contributed to a phallic inferiority complex as another example of biological and cultural interactions, a sense of inferiority from which women are currently struggling to emancipate themselves. The clitoris carries a high erogenous charge in masturbatory activity but is regarded at best as a kind of consolation prize for having lost the penis. It must be added that the psychodynamics of female sexual development are still not very clear. Let me emphasize that I am presenting orthodox psychoanalytic theory because I believe this will provide more cogent insights into the conditions to be discussed.

The pediatrician, gynecologist, and general practitioner will frequently be the first to be consulted for personality behavior and disturbances that disrupt the home or school. Very often such disturbances are associated with fixations at or regression to an earlier psychosexually developmental phase and are no longer age-appropriate. Admixtures of oral and anal manifestations can give rise to wildly inconsistent behavior, and an over-arching unhappiness of the child or adolescent is discernible. It is obvious that there is virtually always a complex interaction between biological, intrapsychic, and situational factors. Developmental processes can be distorted by parental seductiveness, overprotection, hostile rejection, inconsistencies of various kinds, and demands for absolute obedience and compliance. The adolescent's physical and emotional equilibrium can be upset by very neurotic or psychotic parents who create a noxious emotional climate in the home that causes the adolescent to become confused, uncertain of her own normality, guilt-ridden if she is being singled out as scapegoat, and provoked into forms of conscious or unconscious retaliatory behavior that evokes further reprisals from parents. Dysmenhorrea can cause irritability that may trigger off hostile reactions to parents or siblings for real or fancied injuries, usually in an exaggerated explosive form that leaves the adolescent with a residue of guilt. Feelings of social inadequacy may also be displaced to the home, the parents serving as substitute targets for those that cannot be attacked directly.

A major influence at this time, and often more powerful than parental and societal values previously inculcated, are the values and pressures of the peer group. If these values are antisocial, acceptance of them in response to the implied threat of rejection, if refused, can lead to self-destructive behavior involving sexual relations for which there is no emotional readiness, drug abuse, and running away from home. The psychosexual implications of these influences are obvious.

The symptomatic manifestations of psychosexual disturbance in the female adolescent are varied, but problems centering around eating can be considered paradigmatic of regression to a pregenital phase. Hilde Bruch has stated that "Obesity in childhood represents a disturbance in personality in which excessive bodily size becomes the expressive organ of a conflict" (3). This applies to adolescents as well. In such cases it is postulated that the girl's previous repression of her awareness of inner erotic promptings has intensified it, giving rise to greed and insatiability. As Fenichel writes (4), ". . . sexual satisfaction is perceived as a "dirty meal." Periods of depression in which the patients stuff themselves "fat," "bloated," "dirty," "untidy," or "pregnant" and leave their surroundings untidy alternate with "good" periods in which they behave ascetically, feel slim, and conduct themselves normally or with some elation. The body feeling in the "fat" period turns out to be a repetition of the way the girl felt at puberty before her first menstruation, and the spells often coincide with the premenstrual period. The menstrual flow then usually brings a feeling of relief: "The fat-making dirt is pouring out: now I am slim again and will be a good girl and not eat too much."

Psychoanalysis of such patients discloses an intense hatred against their mothers and against femininity, a hatred saturated with fear. Such individuals have little tolerance for separation from mother and create their own baby fat, thicken the body barrier as a defense against sexual penetration, and make themselves unattractive so that boys will shun them. The craving for food represents a craving to get rid of the dangers of femininity, but it also generates guilt feelings because of the unconscious wish to bite and incorporate the mother.

Another problem that is frequently brought to the attention of the physician is anorexia nervosa. Thought at one time to be caused by pituitary anterior lobe insufficiency (1930's), it is today regarded as a psychosomatic entity in which the signs and symptoms of the syndrome have specific meaning to the individual patient. Farquharson and Hyland (5) describe anorexia in the following words:

"The disorder occurs chiefly in adolescent girls, less commonly in men. Following some prolonged emotional conflict, either avowed or concealed, the appetite fails and the intake of food becomes grossly insufficient, leading to loss of weight. Commonly there are mild symptoms such as uneasiness after food, epigastric distress or constipation, which provide a further excuse for anorexia. Emaciation increases and the patient's health becomes an object of great concern to her family. Yet she remains quick, alert, active and restless and with organic disease still able to get about. . . . . When emaciation is greatest, weakness increases and edema of the lower extremities may supervene. Occasionally death results from starvation. Amenorrhea may appear early or only after considerable loss of weight has occurred."

Waller, Kaufman, and Deutsch (7) have elucidated the psychodynamic picture very cogently, emphasizing the "oft-repeated pattern of emphasis on food, alternate over- and undereating, conflict with the family and then precipitation of the syndrome of cachexia with apparent anorexia at the time of adjustment to adulthood and regression to an infantile level." They continue: "This promotes the symbolic equation of eating with sexuality, particularly with the fantasy of impregnation. The overeating and alternating disgust with food represent a shift in the dynamic conflict. In the first, the impregnation fantasy is gratified, while in the second the ensuing guilt and anxiety forbid the intake of food. Other symptoms of the syndrome like amenhorrhea and constipation are also viewed as reflecting the pregnancy fantasy."

The personality structure of these patients is compulsive-obsessive, the somatic factors relating primarily to metabolic changes resulting from starvation and the primary fantasy being considered to center around the significance of oral impregnation. Antecedent psychological events in this condition include conflict between patient and family, preceding history of obesity and overeating, or emphasis upon food and the problems of adjustment at puberty and early adolescence.

By way of a case illustration I recently saw a girl of 16 who complained of abdominal pains and headaches (for which no organic basis could be found). Her menses, which were painful, began at age 12 and stopped at age 14. In the interim she was placed on a 5-day course of hormonal treatment that resulted in only a single menstrual period. She has great concern over her weight, weighs 96 pounds, is very shy and afraid of boys, and is preoccupied with fat and calories. She sometimes has gastric upset and nausea after eating. Her intelligence ranges from bright normal to superior.

Contributing factors comprise mother's pregnancy when the patient was 12 years old and an older brother who has made sexual advances to her.

In the psychological examination she categorized a Fly and Tree as "both can reproduce", and after a mean initial reaction time of 16 seconds for first response to 9 of the cards, she blocked for 1 minute and 40 seconds on one of them and then gave only two responses, "inside of the body, guess it would be the ovaries or the uterus, and this part looks like the head of a fetus", both rather unusual responses and suggesting sex shock involving pregnancy. It is evident that what could become a serious psychosexual disturbance is incubating. From a therapeutic standpoint this has proved a very baffling and often recalcitrant condition, necessitating hospitalization most frequently.

Another case illustration is that of a young woman of 20 who had recently made a suicidal attempt and trailed a history of multiple drug abuse from the age of 16 years. Her main concern at present is her weight, and although she is quite willowy she is afraid of becoming fat.

All indications of sexuality are avoided in her quite bizarre human figure drawing. The male is a nude who is "standing naked and showing his body—it's ugly though," but he regards his body as nice and is thinking "I hope my friends like my body." Marked body preoccupation is patently associated with exhibitionistic impulses.

While drawing a female she bulged out the abdominal area and commented, "She looks pregnant," implying pregnancy fantasies related to her body concern and dieting.

Attachment and separation conflicts predominate in the Rorschach and are coupled with fear of assuming an independent and differentiated self-concept. A traumatic reaction to a card that has a strong sexual pull (normally eliciting such responses as totem pole and animal pelt or an acceptable "penis" percept) is evident from her highly personalized cat "in a lot of pain, looks like it was shocked, looks like in shock," a unique response. The usual female figures in another card perceived as figures playing "some dumb game" and rocking back and forth "like on a rocking horse," and on another card pregnant women who "look really ugly . . . their bodies . . . their faces" underscores fear of pregnancy and retreat from adult femininity that has negative implications for a successful heterosexual adaptation.

The adolescent girl's dissatisfaction with her body, especially as she is developing, is not unusual and frequently works itself out in time. When an adolescent girl insists she is ugly and avoids heterosexual relationships, especially if she is not unprepossessing, fear of males is indicated and there is the probability of a complex relationship with the father that is conducive to psychosexual disturbance.

Sometimes a specific part of the body is singled out for attention. This is true of adolescent girls who demand a rhinoplasty even though the plastic surgeon sees no need for the operation. In cases of this type it has been found that the offending nose represents a displacement from a rejected sex organ which is regarded as ugly and mutilated, the desired operation motivated by the fantasy that alteration of the nose will in some magical way restore body image equilibrium. Sometimes masturbation guilt is also implicated in the problem.

Frank (6) (1967) has made some pertinent points concerning aspects of working with adolescents. He advises the physician to focus upon what has gone wrong and to emphasize to parents that the main task is to find ways to make it possible for the child to function appropriately rather than agonizing over what they have "done wrong." His most cogent statement pertains to the problem of confidentiality and he writes: "No minor should be told that what he confides to the physician will never be revealed to the parents. There are times when the aid of the parents must be enlisted. All that the physician can tell the adolescent is that he will do his best to respect his rights and will use his utmost discretion in handling what is revealed to him. This generally is believable and acceptable."

Most practitioners are or should be competent to render psychiatric first aid dealing with the problems of adolescent girls that come to their attention. When in doubt, a comprehensive psychological evaluation and a psychiatric consultation can ascertain whether psychotherapeutic intervention is necessary. The increasing psychiatric sophistication of physicians warrants the hope that psychosexual disorders of adolescent girls may be prevented or corrected by recognizing early signs, understanding their significance, and taking appropriate action.

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Aids to the Surgeon by Mammography

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The diagnosis of breast lesions by radiographic methods has not met with universal acceptance by surgeons. Their reluctance has arisen primarily because of the realization that errors are still observed and that all lumps, in the opinion of most, must be removed for pathologic examination anyway. Furthermore, virtually all the experience reported has been from the point of view of the radiologist rather than of the surgeon.

However, the overall statistics of false negatives (carcinoma missed) and of false positives (carcinoma diagnosed incorrectly), while they may describe the relative accuracy of mammography, fail to indicate the numerous ways in which the technique can be employed in the diagnosis and management of breast lumps. Radiography can sometimes do what clinical examination cannot, just as it is also true that a clinically suspicious lesion must be removed, no matter what the roentgenologic findings may be. The radiograph cannot replace the microscope, but clinical examination has need of radiologic help.

It is my opinion that mammography has now reached the state which makes it exceptionally useful in diagnosis and necessary, in some instances, for the proper management of breast disease.

Methods of mammography which utilize the instillation of radiopaque material are not included in this report. Nor are the techniques of thermography and xerography considered here, although they may well become standard adjuncts or even replace radiographic mammography because of their safety and clarity. However, the principles involved in their application to the breast are the same as those enunciated in this paper.

Of course, several prerequisites in technique must be fulfilled. For example, special very fine-grained industrial film is needed to show maximum detail. At least three views (cranio-caudal, lateral, and tangential) are required. Time may have to be spent in positioning the patient, in arriving at the optimum exposure, and in making sure that the areas in question are in the radiographic field. But a rapidly increasing number of radiologists have by now acquired the experience and equipment necessary for proper films and for the interpretation of the findings with reasonable accuracy.

In general, the radiologic characteristics of malignant lesions are: 1) pinpoint calcifications and 2) a mass denser than the remaining tissues of the breast, with spicules proceeding outward, or with surface irregularities that have an occasional larger spicular process.

Mammography is of greatest aid to the surgeon who has a clear concept of how he can be helped by x-rays of the breast. Roentgenography can be used: a. To aid in the management of established breast lesions; b. To search for a lesion

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when symptoms or signs point to the breast; and c. To search for a lesion when no symptoms or signs are present in the breast.

A. Aid in Management of Established Breast Lesions.

1. *Multiple lumps.* When several nodules are present in the same or both breasts, the question of which mass is to be removed and which is to be left behind is often difficult to answer. X-ray films can sometimes place doubt concerning one of the multiple nodularities that clinical examination cannot elicit (Fig. 1).

2. *Repeated appearance of lumps.* X-ray studies can forestall the repeated removal of lumps which continue to appear. One may be faced with the prospect of excising each and every nodule as it is found or else one can use the x-ray to help to indicate benignity or similarity to masses previously removed. Of course, if clinical suspicion exists concerning any lump, removal is mandatory.

3. *Small malignant tumor hidden by benign lesion.* A benign cyst, fibroadenoma, or lipoma can cover a deeper lesion that cannot be detected on palpation either preoperatively or even at the operating table after the benign lesion has been removed. In these instances, the x-ray technique can be more informative than a surgical exploration. It prevents the excision of a benign tumor while an adjacent malignant lesion remains undetected (Fig. 2).

4. *Cysts.* In addition to revealing lesions hidden by the cyst, mammography can give security to the surgeon who wishes to manage a cyst by aspiration. Having the films taken before aspiration will prevent false pictures caused by the occasional bleeding into the cyst or surrounding tissues accompanying the aspiration. On the other hand, aspiration first with the introduction of a small amount of air directly before mammography will show the cyst wall lining and detect irregularities of suspicious projections. I am not sure which is the better regimen, but either method is valuable.

5. *Biopsy not feasible.* If biopsy of a lesion is impossible or inadvisable for a variety of reasons (e.g., unusually advanced age, marked debility, refusal by patient), mammography can help to indicate whether the lesion is clearly benign, unequivocally malignant, or indeterminable without surgery. Errors may be made here, too, but when the clinical impression and radiologic findings agree, correct diagnosis is more likely and the management of the patient on firmer ground.

6. *Confirm clinical impression of carcinoma.* Sometimes this can be of help to the surgeon in arranging for admission, planning a schedule, or preparing the patient and family. However, for the performance of a mastectomy, a tissue diagnosis—not the radiograph (no matter how clear cut)—is mandatory, in the present state of knowledge.

B. Search for Lesion—When Symptoms or Signs Are Present.

1. *Vague palpable thickenings.* The combination of clear-cut, clinically benign characteristics and unequivocal evidence on x-ray of the absence of malignancy gives support to the continued non-operative observation of breasts,

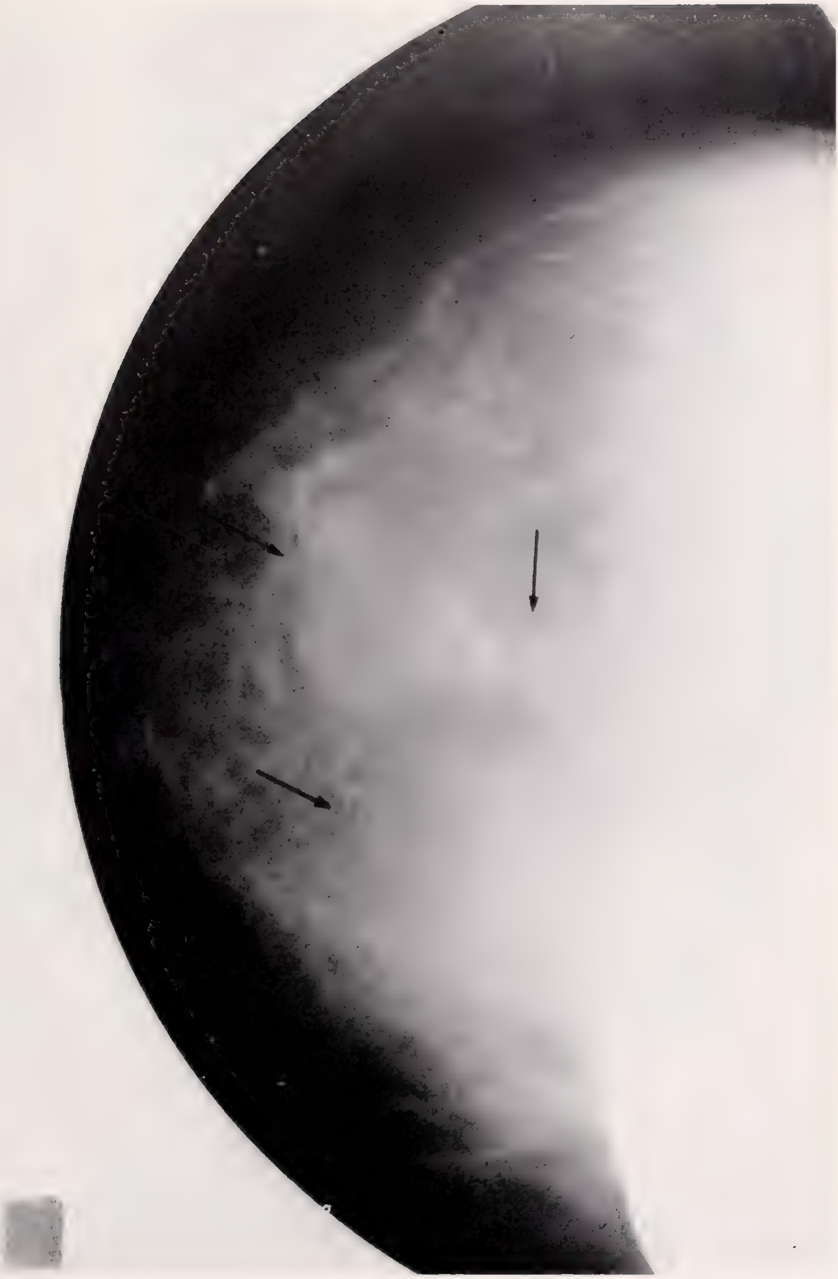

FIG. 1. X-ray shows 3 lesions—Two fibroadenomas and one carcinoma which was also felt to be benign clinically. Film indicated clearly which of the 3 required biopsy.

especially when doubt exists about the actual presence of any abnormality. On the other hand, suspicious characteristics on roentgenogram or visualization of an unsuspected malignant lesion can direct the surgeon precisely to the area needing biopsy.

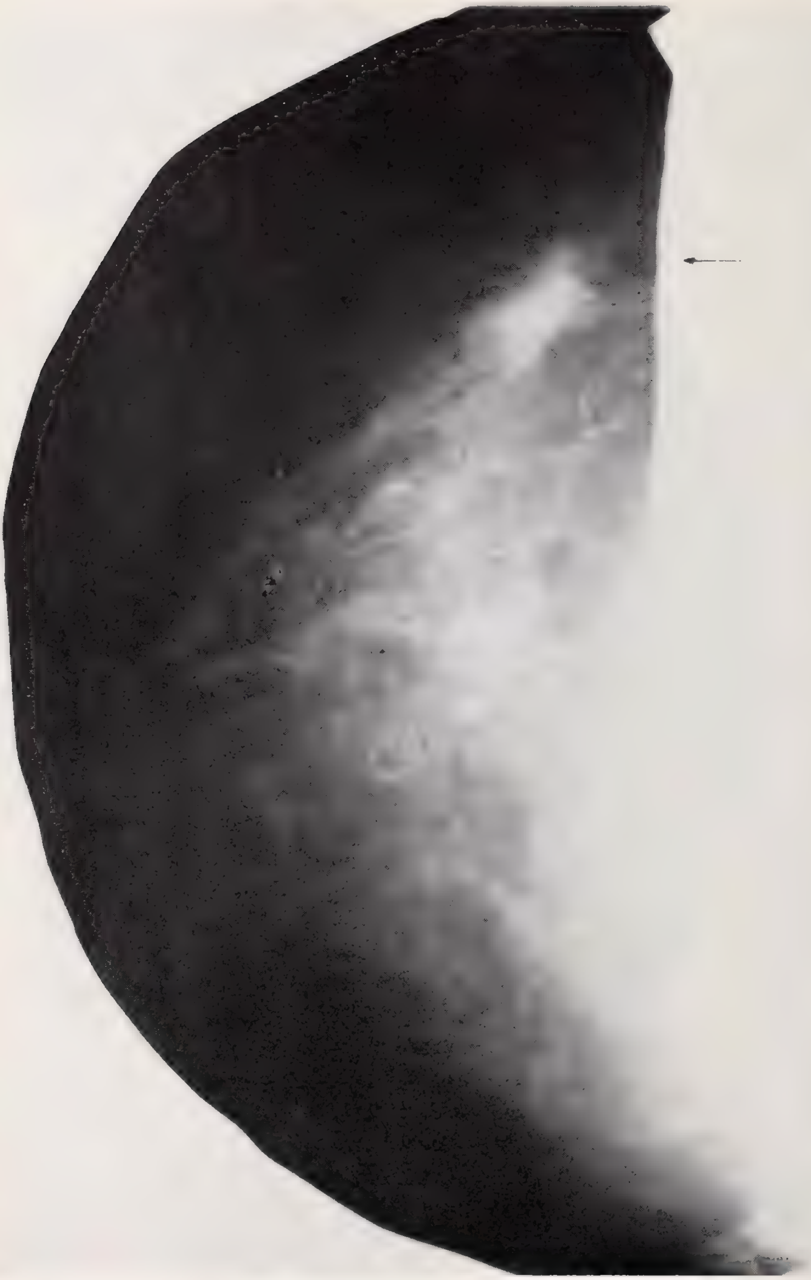

FIG. 2. Carcinoma, not detectable clinically, covered and hidden by large lipoma. At operation, after excision of lipoma, breast tissue beneath was biopsied and radiologic finding confirmed.

2. *Nipple discharge.* When the source of a bloody discharge is not detectable by physical examination, mammography may reveal an impalpable density near or deep to the areola, although radiography has not often been contributory when the nipple discharge is unaccompanied by a palpable mass, since the source is usually inside the ducts. I have had no experience with instillation of radiopaque media into the ducts.

3. *Pain in the breast.* Before dismissing a patient with pain in a breast which contains no nodules or other sources of symptoms, x-ray films give added clearance. Unexpected, early malignant lesions can be detected which escape all other clinical means of discovery (Fig. 5).

4. *Metastatic carcinoma in axillary nodes.* The question of what to do about the breast in which no lesion is palpable but whose axillary node contains carcinoma can sometimes be answered by mammographic demonstration of a malignant lesion.

5. *Unexplained skin lesions or erythema.* The search for deep-seated impalpable neoplasms is facilitated by x-ray survey of the breasts.

6. *Paget's disease of the nipple.* The x-ray can sometimes reveal the underlying carcinoma which escapes clinical detection. Of course, a proved pathologic diagnosis of Paget's disease of the nipple requires a mastectomy even with a normal mammogram.

C. Search for Lesion when Symptoms and Signs are Absent.

1. *Status of opposite breast in preoperative breast carcinoma.* Mammography can reveal concomitant carcinoma in the breast opposite the side in which carcinoma is clearly present. This will prevent mastectomy on one side, while leaving inadvertently another undetected malignancy (Fig. 3).

2. *Status of remaining breast after mastectomy.* X-ray films can aid in following the remaining breast after mastectomy in order to detect early the occurrence of a second carcinoma (Fig. 4).

3. *Search for primary lesion.* When distant metastases have an unknown origin, mammography is a useful tool in seeking the primary source.

4. *Voluminous breasts.* Exceptionally large, voluminous breasts can conceal malignant lesions which are undetectable by physical examination but which are discernible by x-ray study (Fig. 5).

5. *Screening.* In the future, mammography may be used for routine screening of all women over a certain age. At the present time, this is not advocated unequivocally because the final conclusion is not yet available on how often such scout films would be needed to be effective nor on how safe yearly routine studies would be. Nevertheless, studies by The Public Health Service and others, notably Shapiro, Strax, and Venet (1) have shown the exceptional usefulness of regular radiographic screening.

6. *Management of cancerophobic patient.* Mammography has occasionally been effective in reassuring people who are obsessed with fear and in whom no clinical evidence exists of a lump in the breast. Of course, it can also help force the surgical biopsy of a lesion which the patient is reluctant to have operated upon.

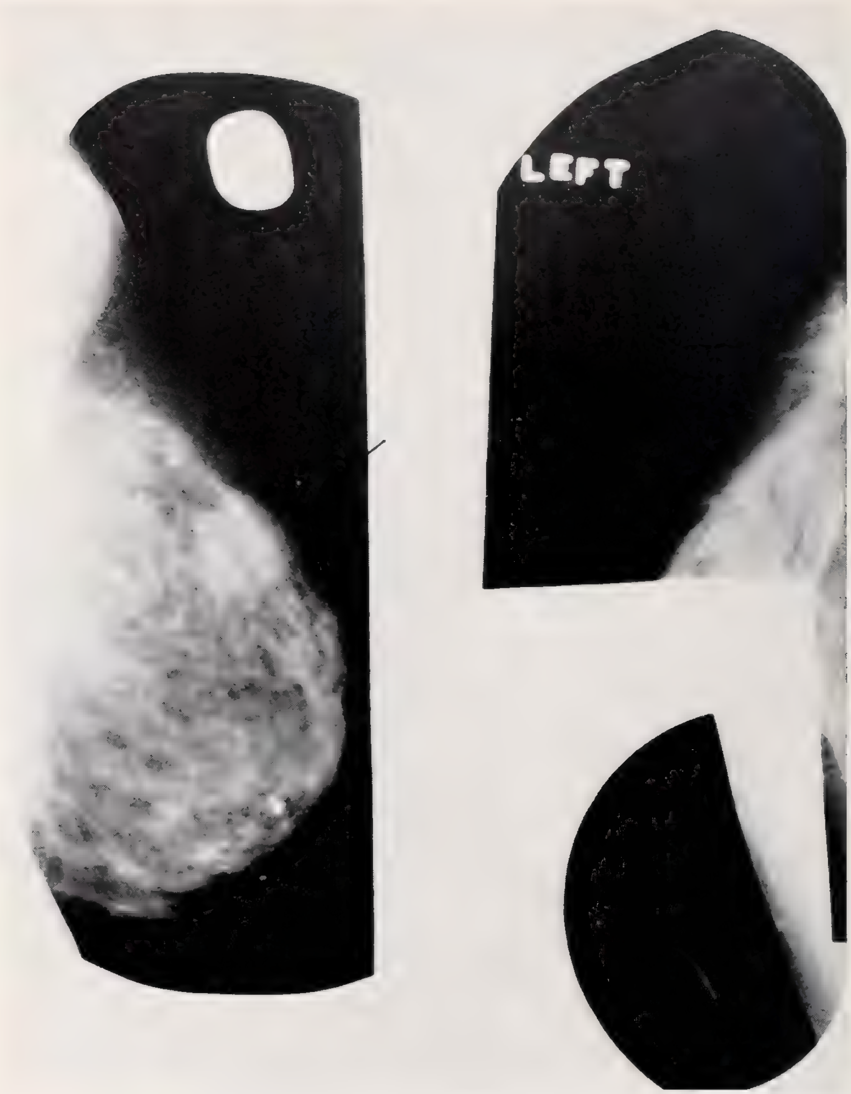

Fig. 3. Preoperative films confirmed clinical diagnosis of carcinoma in right breast, but also revealed carcinoma in left breast which was missed on clinical examination because it was small, high in the breast and close to the chest wall.

Discussion

In advocating the frequent employment of mammography, one must also be mindful of its limitations and of its pitfalls. For example, fine calcific clusters without a palpable nodule, which are not given clearance by the radiologist, can present a new problem which is in a sense created by the radiograph itself, because the surgeon is then bound to excise or biopsy the area in question. Sometimes considerable effort and concentration are needed to map out precisely the

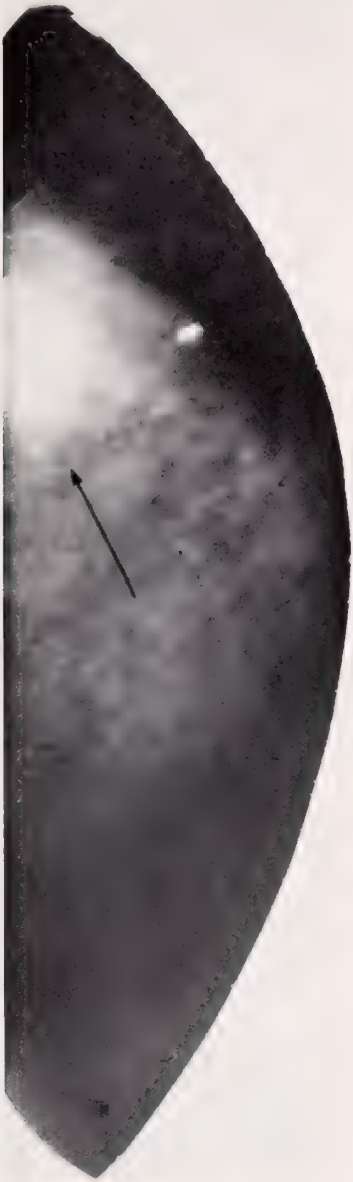

FIG. 4. Medullary carcinoma in remaining breast 2 years after mastectomy.

exact location and depth of the cluster, so that the excision of this segment can be accomplished. If feasible, radiography of the tissue after its removal will demonstrate immediately whether the questionable area is contained in the excised specimen. But even without the facilities for immediate checking by x-ray, careful cooperation between the surgeon and radiologist can usually determine the exact boundaries and location of the segment to be excised.

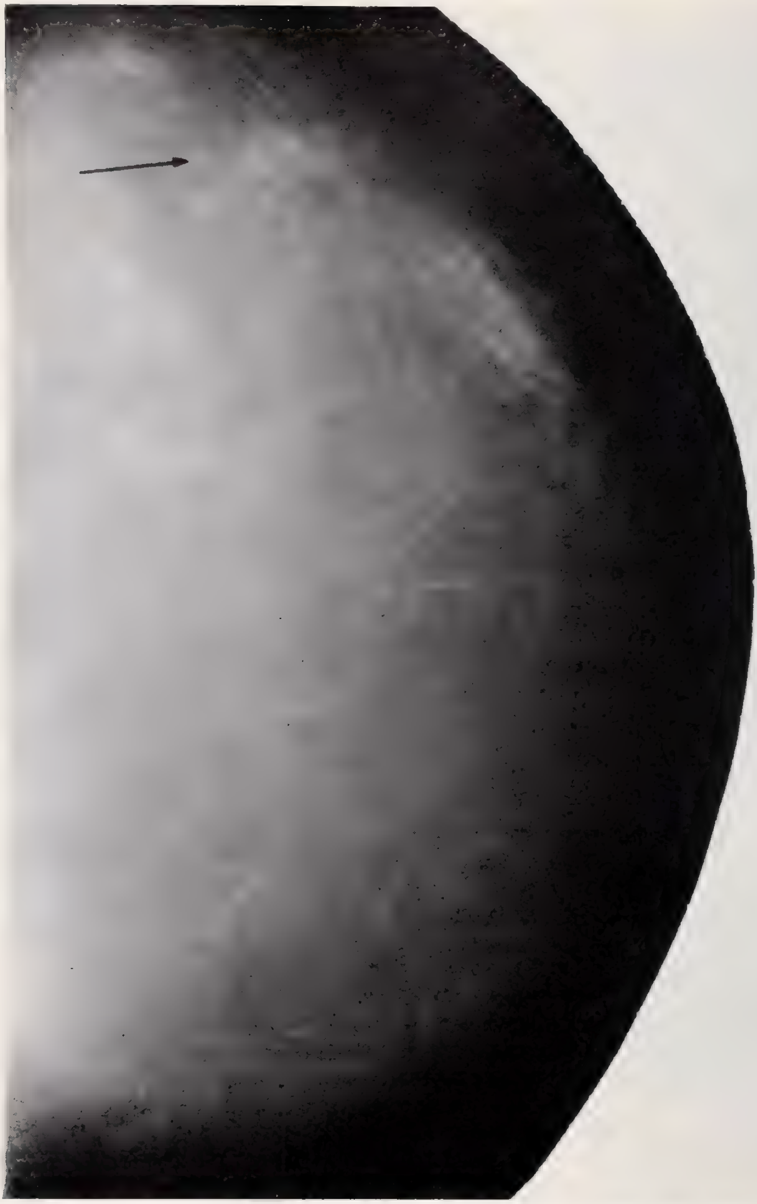

FIG. 5. Survey film showed small carcinoma. No mass was palpable clinically, at operation, or even by pathologist after wedge resection of breast for frozen section. Serial sections finally revealed the carcinoma.

As more experience accumulates in correlating radiographic observations with pathologic study, fewer such doubtful, benign areas are likely to be encountered. However, even if it should turn out that among these excised specimens only an occasional malignant tumor is discovered, it will surely have been worth while to search for the clinically impalpable carcinoma.

Percentages of error have declined with the passage of time and the acquisition of experience. Warren (2) found that 8 percent of carcinomas were missed on roentgenologic examination. Gershon-Cohen (3–5) reported errors of 5 per cent. In a series of 2, 522 mammograms reported by Egan (6) without any previous clinical data, 96.7 per cent of the carcinomas and 91.6 per cent of the benign lesions were diagnosed correctly. On the other hand, in routine radiologic screening of breasts by radiologists with minimal experience, errors can be high.

Zuckerman (7) has pointed out the problems of interpreting the statistical reports of accuracy. For instance, some roentgenologists advise biopsy whenever any unusual variations are seen. This would lead to a high false positive ratio and a low false negative figure. Others prefer to take a position only on unequivocal findings, with a correspondingly low false positive percentage but a higher false negative number. Also, the percentages of accuracy may depend on the source of the cases, for in a cancer institution, a larger proportion of clear-cut carcinomas is more likely to be found than in an office practice.

Summary

Mammography is a valuable adjunctive to the surgeon in the diagnosis and treatment of breast lesions by aiding in the management of established breast tumors, in the search for lesions when symptoms point to the breast although no mass is palpable, and in surveying the breast when symptoms and signs are absent. In addition to special film, careful technique, and an experienced radiologist, an understanding on the part of the surgeon of how mammography can help is a prerequisite for proper use of the method.

Acknowledgment

The mammograms used in this report were taken by Dr. Herman Zuckerman.

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Chondroblastic Sarcoma of the Breast

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Abstract

A primary chondroblastic sarcoma of the breast, occurring in a thirty-nine-year-old Chinese woman, is presented. Whereas chondrosarcomatous differentiation is well known in malignant stromal tumors of the breast, the presence of malignant chondroblastoma is most unusual. The tumor pursued an aggressive course with a rapidly fatal termination.

Primary osseous and cartilaginous tumors of the breast occur infrequently (1). Bone and cartilage do appear within a variety of breast neoplasms either by epithelial metaplasia or focally within benign or malignant stromal tumors including cystosarcoma phyllodes (2 4). We have found no previous record of chondroblastomatous differentiation within a mammary tumor. The ensuing report will document such an occurrence.

Case Report

Clinical Data: A thirty-nine-year-old Chinese woman noted a breast mass one and a half months prior to admission. Chest radiography did not reveal any pulmonary involvement. A modified radical mastectomy was performed. Three months following surgery radiologic evidence of pulmonary metastases was present, and she died in the ninth postoperative month with multiple nodules in both lungs. An autopsy was not obtained.

Pathological Findings: The tumor measured 5 × 4 cm. Microscopically sheets of uniform polygonal cells with clear cytoplasm were seen (Figs. 1, 2, 3). Nuclei were small and pyknotic (Fig. 3). Mitotic activity varied in different areas of the tumor. Multinucleated giant cells of osteoclastic type were dispersed throughout the tumor (Fig. 1). Differentiation into nodules of frankly chondroid structure was evident (Fig. 2), with spotty calcification of many foci. In addition, osteoid was also formed (Fig. 4).

Comment

Osseous and cartilaginous tumors of the breast are rare. Chondroma, osteochondroma, chondrosarcoma, osteochondrosarcoma, osteosarcoma, and giant cell sarcoma have previously been recorded (1). Cartilaginous metaplasia has been described in a small percentage of cystosarcomas (3 4).

The occurrence of a breast tumor primarily chondroblastomatous in nature has apparently not been previously noted. Chondroblastomas are generally limited to regions of immature cartilage formation, predominantly the epiphysis in children, and, though usually benign, may metastasize (5). Chondroid mammary tumors occur over a wide age range and have a prognosis reflecting the tumor type (1, 2). Chondroid differentiation within a cystosarcoma, an event reported in women primarily in the fourth and fifth decades, does not appear to

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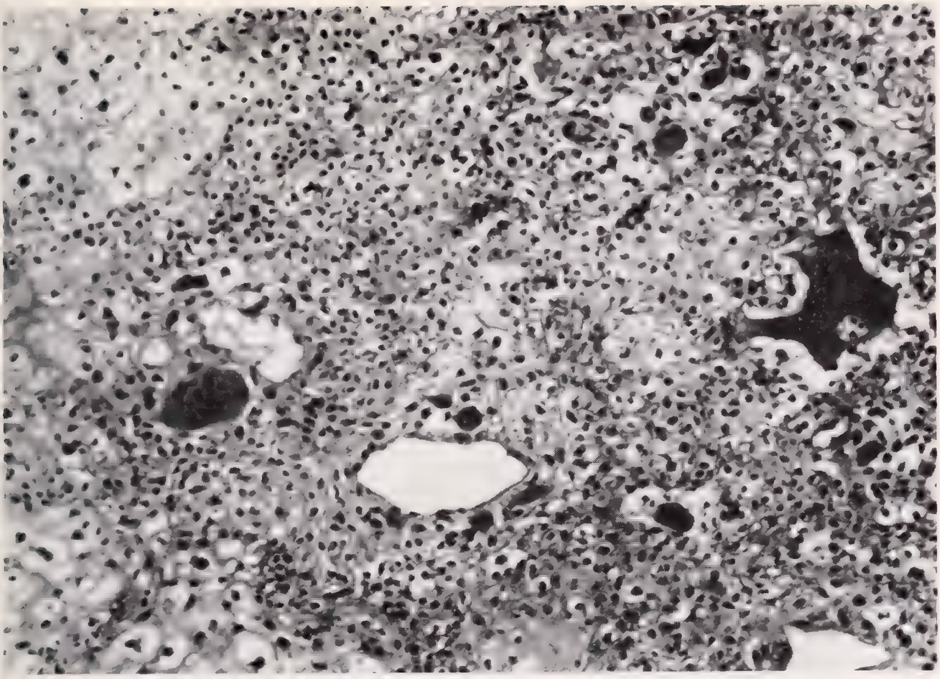

Fig. 1. Low-power micrograph showing sheets of polygonal cells and giant cells of osteoclastic type H&E × 80.

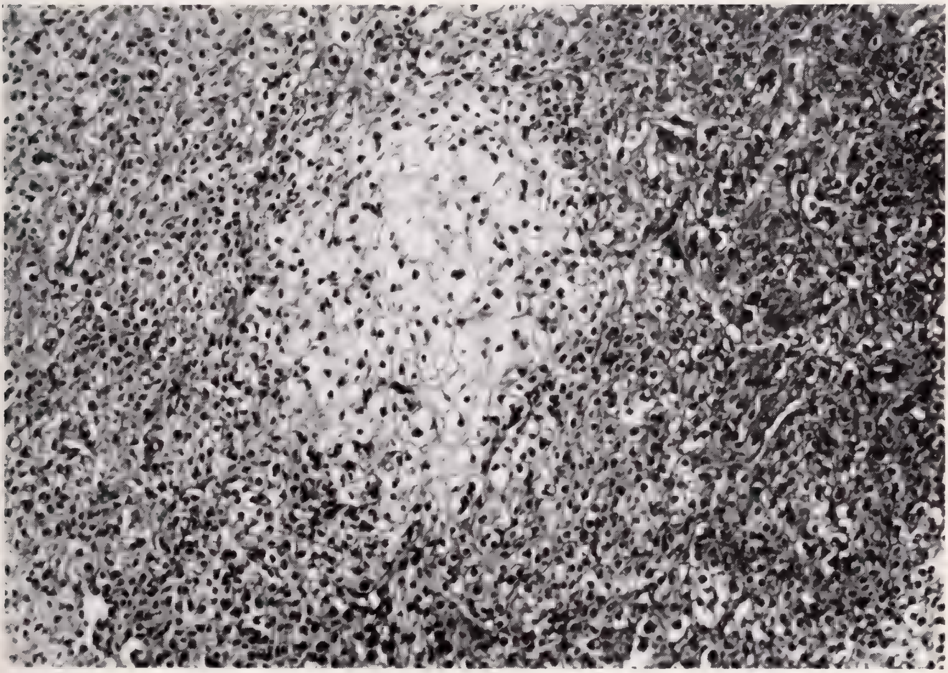

Fig. 2. Low-power micrograph showing a focus of frankly chondroid differentiation H&E × 80.

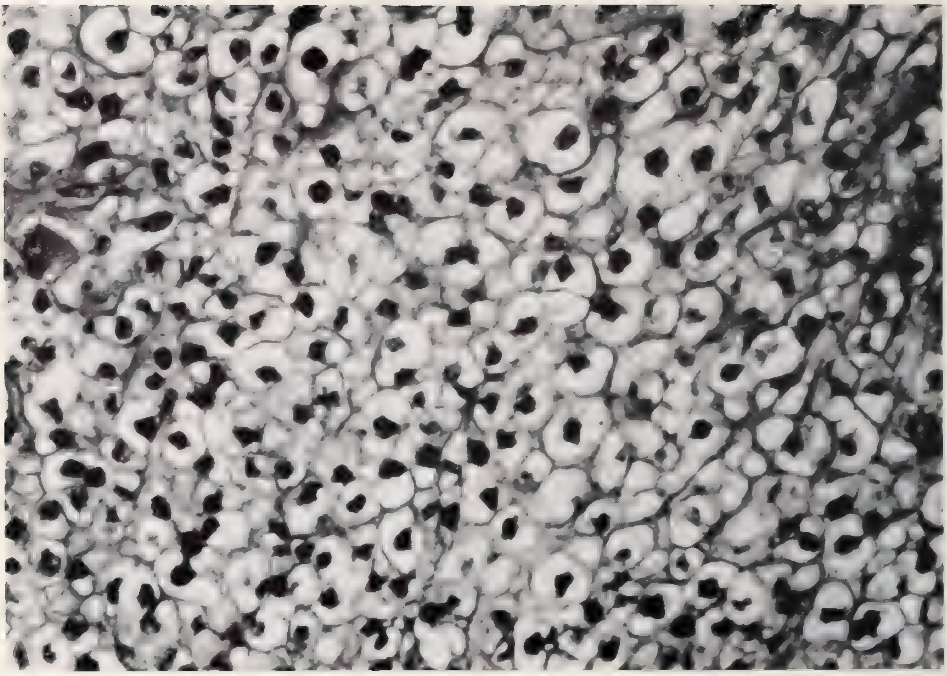

FIG. 3. High-power micrograph showing polygonal cells with clear cytoplasm and pyknotic nuclei H&E × 200.

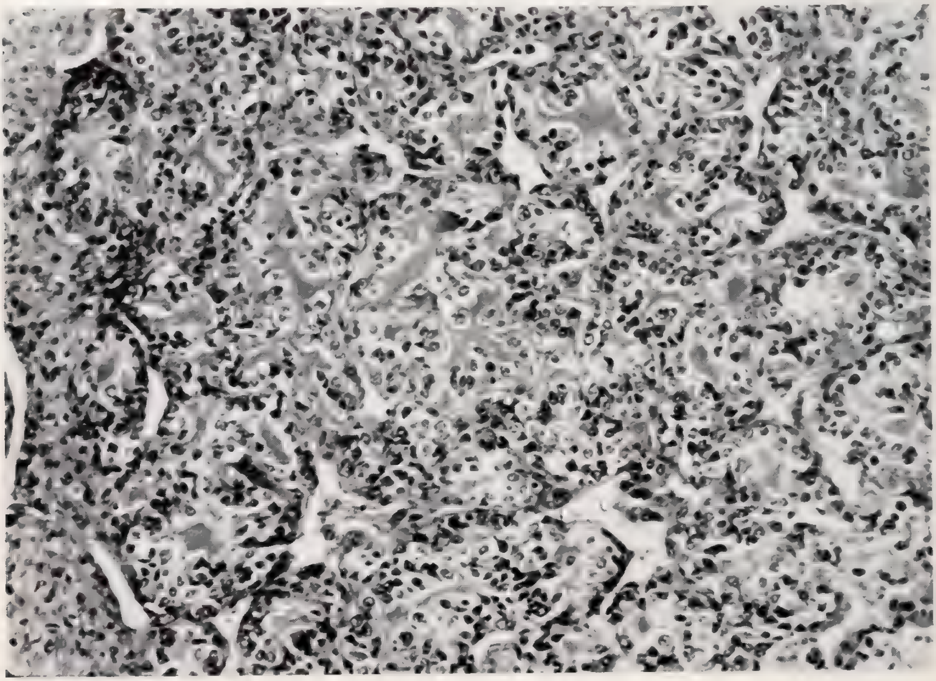

FIG. 4. Low-power micrograph showing osteoid formation H&E × 80.

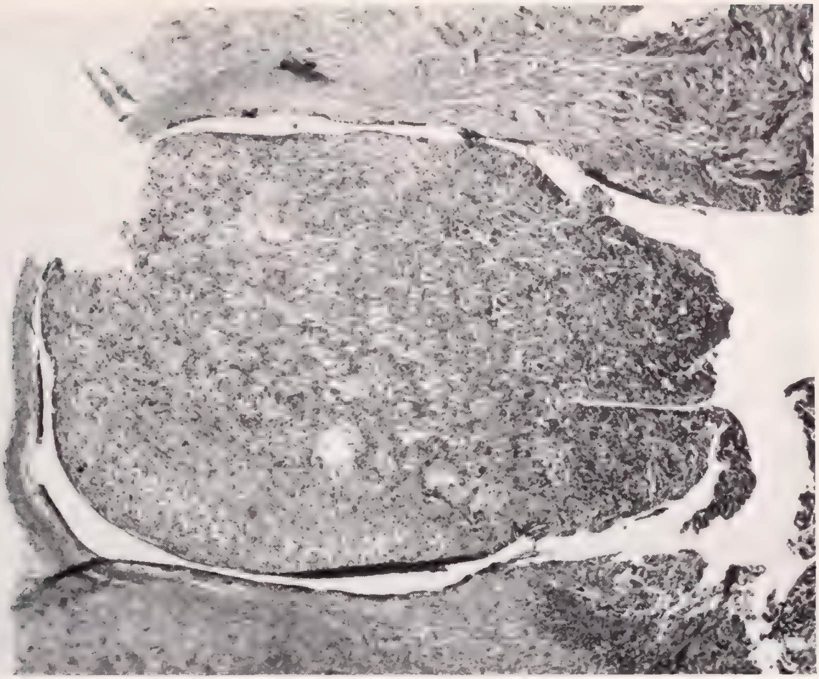

FIG. 5. Low-power micrograph showing an intracanalicular growth pattern H&E × 20.

affect the prognosis, as both benign and malignant cases have been noted (3, 4). The two documented metastasizing cystosarcomas with chondroid differentiation have both taken considerably longer periods of time to disseminate than did the tumor under discussion (4).

Many bony, cartilaginous, and stromal sarcomas have been considered to arise in fibroadenomas (1). Origin of the tumor under consideration from a cystosarcoma phyllodes may be suspected on the basis of a single focus in which an intracanalicular growth pattern was observed (Fig. 5). However, only one such area was found in multiple sections, and an unequivocal statement cannot be made in this regard.

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The Value of Exploratory Laparotomy in Fever of Unknown Etiology

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Fever of unknown origin presents a diagnostic challenge to the physician. The criteria for fever of unknown origin were well laid out in the classic report of Petersdorf and Beeson (1). Stated they are: an illness of three weeks duration or longer, a temperature over 38.3°C (at least on some occasions), and hospitalization of one week with extensive tests. Multiple laboratory tests, X-rays, radioactive scans, tissue biopsies, serologic studies, and other approaches may be utilized to reach a diagnosis. In addition exploratory laparotomy has been advocated as a diagnostic procedure and its usefulness in the work-up of fever of unknown origin will be discussed.

Petersdorf and Beeson reported the results of a prospective study of 100 cases of fever of unknown etiology, and discussed the etiology and means of arrival at diagnosis. Infections (40%), neoplasms (20%), and collagen vascular diseases (15%) constituted the main etiologies. In 23 cases the cause was established by needle and excisional biopsy, and in 15 cases exploratory laparotomy established the diagnosis. In 8 cases in which one or more biopsies were negative the diagnosis was made at laparotomy. In 7 cases of biliary tract disease or liver infections the diagnosis was made in 4 cases at laparotomy and in 2 cases at autopsy. One case at autopsy was empyema of the gallbladder. The study points out the fact that biopsy and laparotomy are useful in arriving at a definitive diagnosis in fever of unknown origin.

The usefulness of laparotomy may be measured by the retrospective study of Geraci et al (2) in a series of 70 patients with fever of unknown origin in whom laparotomy was performed. A definitive diagnosis was made in 60% of the cases. In 21 patients malignant disease was the cause, including 10 cases of lymphoma. Fifteen patients had infectious etiologies and 5 of these were tuberculous peritonitis. An unusual difference between this and other studies was that, after repeated observations and extensive investigations, 30 of the 70 patients had no objective findings pointing to the abdomen as the site of the pathology. However, the authors pointed out that evidence of continuing loss of weight, high sedimentation rate, and progressive anemia aided in their decision to operate.

In a study by Baker et al (3) of 28 patients who underwent exploratory laparotomy for fever of unknown origin, an attempt was made to correlate signs and symptoms referrable to the abdomen prior to the laparotomy with positive findings at surgery. A point system was utilized where one point was assigned to each symptom (abdominal pain, diarrhea, or abdominal distention), positive physical findings (tenderness, palpable liver, palpable spleen) and positive lab findings

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(elevated alkaline phosphatase, bilirubin, or amylase or BSP retention) as well as any x-ray which would suggest intraabdominal disease. Surgery produced a diagnosis in 57% of the patients. All patients with positive laparotomy findings had at least a score of one. Six patients had a rating of zero and all of these patients had a negative laparotomy. Neoplasm (3 cases), infection (6 cases), and collagen-vascular diseases (4 cases), sarcoidosis (2 cases) and regional ileitis (1 case) represented the breakdown of the cases established at laparotomy. The authors felt that, if there was no indication for abdominal pathology, the period of observation should be prolonged and exploratory laparotomy should be performed only after the patient began to deteriorate.

Keller and Williams (4) reported the results of a series of 46 patients with fever of undetermined origin in whom laparotomy was performed. Positive findings were established in 82%. There were 9 patients with lymphoma, 10 with carcinoma, 14 patients with inflammatory disease including 5 patients with disseminated abdominal tuberculosis and 5 patients with miscellaneous causes of fever. Physical findings of splenomegaly or hepatomegaly had a high correlation with positive laparotomies. The one most helpful laboratory value was elevated alkaline phosphatase. Seven out of 8 patients with high alkaline phosphatase had a diagnosis made at laparotomy.

The Keller (4) and Geraci (2) studies revealed a large number of cases of tuberculosis found by laparotomy. Tuberculosis is one of the major infections to be considered among the cases of fever of unknown origin. When present it is often in the miliary form. The tuberculin skin test may be negative and pulmonary lesions absent (5, 6). Needle biopsy with culture of the liver may be helpful (7, 8). However, in the reports by Keller and Geraci extensive studies were performed, including needle biopsies of the liver, without yielding a diagnosis prior to laparotomy.

In a Scandinavian study by Barr et al (9) of 14 cases of fever of unknown origin the authors recommended a biopsy scheme during a laparotomy where gross findings were not evident. They included removal of specimens of liver, mesentery and omentum, needle sample of the spleen, and removal of lymph nodes including the retroperitoneal area. They based this protocol on the success of obtaining a diagnosis in one case of giant cell arteritis although the abdominal cavity was grossly normal.

Other less invasive techniques may be considered before exploratory laparotomy in patients with fever of unknown origin. Liver scan is helpful in delineating disease of the right upper quadrant. Needle biopsy of the liver had already been mentioned as useful in determining extrapulmonary tuberculosis and it aids in confirmation of lymphoma, sarcoidosis, histoplasmosis, brucellosis, and schistosomiasis. Multiple tissue biopsies of bone marrow, lymph nodes, muscle, and temporal artery may be helpful. Simultaneous liver and lung scans aid in establishing subphrenic abscess.

Therapeutic trials may be considered in patients in whom no diagnosis has been made after extensive studies. In general blind trials do more harm than good.

Antituberculous therapy may be utilized when tuberculosis is suspected. Broad spectrum therapy is contraindicated because it usually yields no valuable information.

After a patient has undergone extensive studies, exploratory laparotomy seriously should be considered rather than institute unfounded drug therapy. Indications for laparotomy increase if the patient has been debilitated for a prolonged period of time or if the patient is beginning to deteriorate. Further x-rays and tests may consume valuable time while yielding diminishing returns, whereas laparotomy may provide a definite diagnosis. Laparotomy appears to be especially indicated when the data point to the abdomen as a possible site of pathology. The literature cited provide evidence in support of the value of laparotomy in fever of unknown origin. More studies are needed, however, because most studies have been retrospective and based on somewhat small sample sizes.

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Modern Concepts in the Management of Gastrojejunocolic Fistula

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Introduction

Gastrojejunocolic fistula complicates stomal ulceration in approximately one in seven patients, with a reported incidence varying from 6.6–22.4% (1). Six years is the average time lapse between surgery for peptic ulceration and the onset of gastrojejunocolic fistula when this occurs (2, 3).

This is the report of a case in which endoscopy and the estimation of serum gastrin were of great value in planning treatment. Furthermore, intravenous hyperalimentation during the preparation of the patient was a great benefit.

Case Report

A 49-year-old man was admitted in June 1974 with a six-month history of diarrhea. He had five or six loose bowel movements each day and, in addition, noted an annoying inconstant lower abdominal pain which radiated to his back, a bad taste in his mouth, and a 34-pound weight loss in the preceding two months.

The history included nine previous hospital admissions at other institutions. In 1968 he had a strangulated right inguinal hernia repaired. In 1969 he developed duodenal and prepyloric ulcers with melena, for which he was hospitalized and treated medically. He was well until November 1970 when he suffered a perforation of a sigmoid diverticulum which was drained. After a month's stormy postoperative course, a transverse colostomy was fashioned. In January 1971 he had a resection of the sigmoid colon and three months later his colostomy was closed. No sooner had he recovered from this series of operations when a carcinoma appeared on the right side of the floor of the mouth. After a course of radiotherapy, in September 1971, he had a right radical neck dissection, excision of the floor of the mouth, partial mandibulectomy and partial glossectomy. Six months later he developed abdominal pain, collapsed following hematemesis, and was hospitalized. After two further episodes of bleeding, a subtotal Billroth II gastrectomy, with an antecolic gastrojejunostomy, was performed in June 1972. He was well until about six months prior to his admission to this hospital in June 1974.

On admission, he weighed 98 pounds and appeared cachectic. As a result of multiple previous operations, he had several incisional herniae, and a generally thin and weakened abdominal wall. No abdominal masses were palpable.

Laboratory data included Hb 11.3 gm %, WBC 6,600 per cu mm, normal electrolytes, BUN 15 mgm %, total protein was 5.2 gm %, albumin 3.9 gm %, alkaline phosphatase 15 mU/ml, lactic acid dehydrogenase 350 units, serum glutamic oxalate transaminase 44 mU/ml, serum glutamic pyruvate transaminase 19 mU/ml, fractionated lactic acid dehydrogenase 350 units, serum calcium 8.4 mgm %, phosphate 2.2 mg %, urinary calcium 237 mg/24 hour and urinary phosphorus 505 mg/24 hour. During his course in the hospital, the Hb fell to 9.8 mg %, requiring preoperative transfusions. The serum proteins, and calcium and phosphorus all returned to normal. Liver function tests fluctuated minimally from the initial levels but did not return to normal. A liver biopsy showed chronic hepatitis. The Australia antigen test was negative. Glucose tolerance was not done because he was on hyperalimentation.

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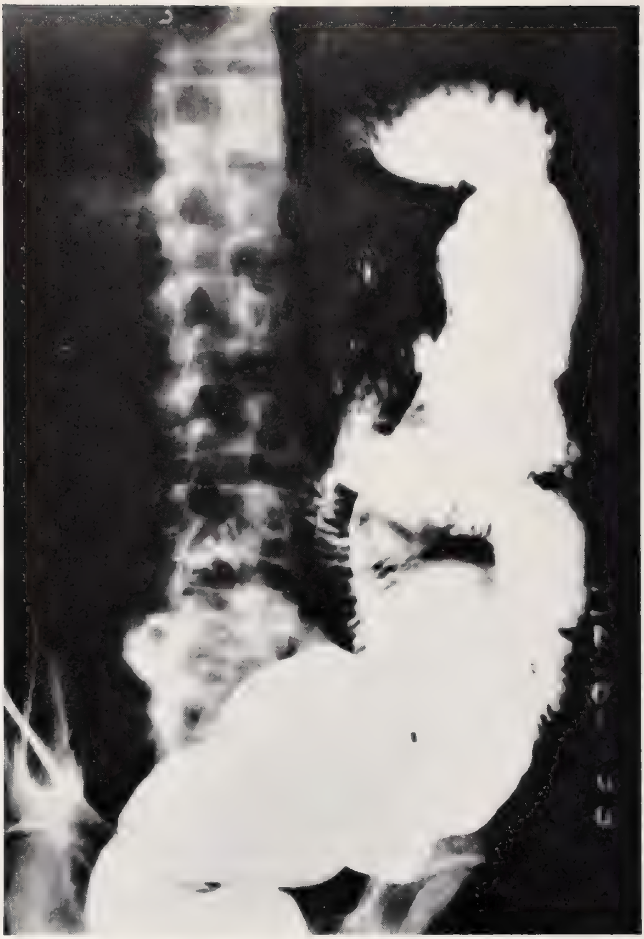

FIG. 1. Barium meal demonstrating a gastrojejunocolic fistula. The stomach, small intestine and colon fill immediately.

Gastric analysis gave a pH of 1, no bile, a free acid of 46 mEq/L, total acid of 116 mEq/L, positive guaiac and a volume of 800 cc in 12 hours. Serum gastrin was 20 picograms per ml.

A barium meal and a barium enema demonstrated his gastrocolic fistula (Fig. 1). Gastroscopy showed mild inflammation at the gastroenterostomy, which opened to reveal a large cavity leading to the colon. Feces were present in this cavity. The cavity itself was really an anastomosis so that, in effect, the afferent loop of jejunum opened into, and the efferent loop opened from, the ulcer. These loops of jejunum did not appear unduly inflamed. The colon was easily entered through the ulcer crater and appeared normal. Colonoscopy also confirmed the presence of the gastrojejunocolic fistula.

The patient was managed by intravenous feeding for one month, receiving amino acid and glucose sufficient to supply 3500 calories per day. During this time his weight increased to 107 lbs. The foul taste in his mouth and his diarrhea stopped.

At operation there was an inflammatory mass involving the gastrojejunostomy which extended to the anterior abdominal wall and posteriorly included a segment of transverse colon. The lumen of the stomach, small and large bowel were completely clean as a result of the parenteral alimentation. It was therefore possible to perform a bilateral truncal

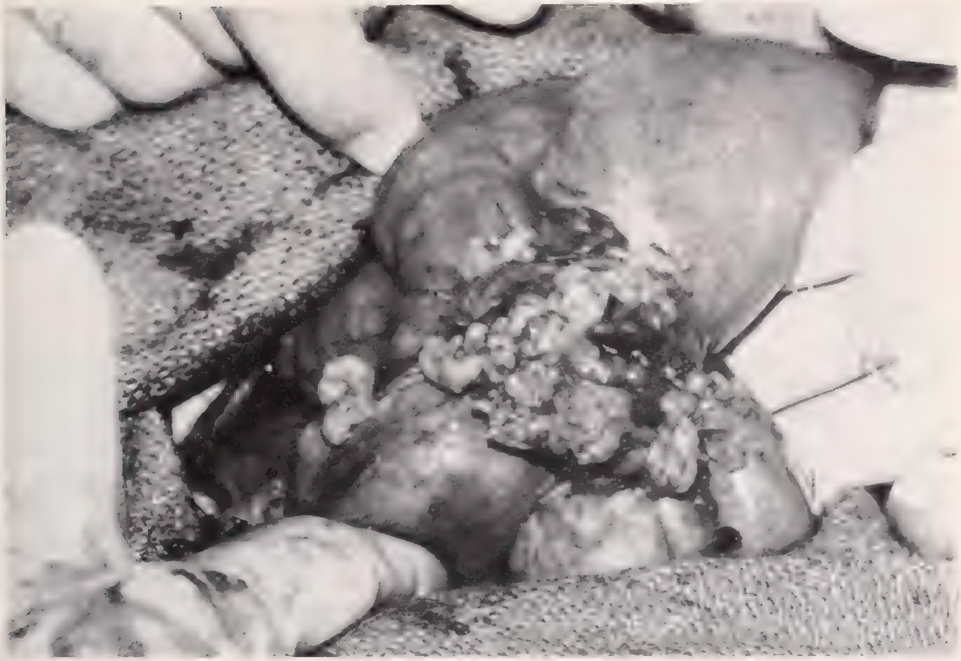

FIG. 2. Operative photograph of the gastrojejunocolic fistula.

vagotomy, and resect the gastrojejunostomy with a portion of stomach, segments of the afferent and efferent jejunum and a cuff of transverse colon all in one stage (Fig. 2). Colocolic, jejunojejunal and gastrojejunal anastomoses were effected. He made an uneventful recovery.

Incidence and Etiology

Approximately 95% of stomal ulcers follow surgery for duodenal ulcer, and the remaining 5% follow procedures for gastric ulceration or combined gastric and duodenal ulceration (3, 6). Wychulis et al (3) in their review found that stomal ulcers appear earlier after subtotal gastric resection for duodenal ulcer than after gastroenterostomy alone (Table I).

The most obvious cause of stomal ulceration which proceeds to the complication of gastrojejunocolic fistula is the Zollinger-Ellison syndrome. High acid due to high gastrin levels from a retained antrum, or remotely, a hormone secreting

TABLE I

Interval from Initial Operation to Onset of Stomal Ulceration (3)

Operation	Interval (years)
Gastroenterostomy	7.4
Gastric resection	1.9
Gastroenterostomy and vagotomy	1.7
Gastric resection and vagotomy	1.1

bronchogenic carcinoma must be excluded. A high gastric acid is more likely to occur with a large parietal cell mass, even if, as in our case, a subtotal gastrectomy is said to have been performed previously. On the other hand, a high gastric acid could be a response to neuronal stimulation through the vagi. Sometimes it follows hyperparathyroidism. With normal acid levels, the cause could be an excessively long afferent loop or chronic pancreatitis, so that bicarbonate levels at the gastrojejunal stoma are reduced. With low acid levels, cancer of the stomach is the most likely cause of gastrojejunocolic fistula.

Diagnosis

The typical symptoms are persistent diarrhea, fecal vomiting and loss of weight. Epigastric pain is inconstant but may be worse than the original ulcer pain. There may be abdominal tenderness or a mass, but half the patients present with no abnormal signs (2). Frequent laboratory findings include anemia, low serum proteins, low calcium, evidence of vitamin deficiencies and disturbance of electrolyte balance (7).

Gastric acid levels are best investigated by an overnight collection, taking care with the positioning of the nasogastric tube. Insulin test should be used to check the completeness of any previous truncal vagotomy. If facilities are available, a serum gastrin should be done, for normal levels will exclude the Zollinger-Ellison syndrome, a retained antrum and a gastrin-secreting bronchogenic carcinoma. Liver function should be investigated since poor liver function may result in inability to metabolize gastrin and secretin, which would result in increased blood levels for these hormones.

When the preceding investigations have been completed, and if they were normal, chronic pancreatitis can be excluded by the secretin test. Hyperparathyroidism and insulinoma must be excluded by study of calcium and carbohydrate metabolism.

Because the flow of gastrointestinal contents is from the colon into the jejunum or stomach, with accompanying intestinal infection and diarrhea (2), a barium enema is more likely to show a gastrocolic fistula than a barium meal (8).

Endoscopy

With the advent of fiberoptics at the beginning of this decade, endoscopy has come into its own. Using an end-viewing instrument, the gastrojejunal anastomosis may easily be entered, so that ulceration and fistulae are readily diagnosed. Once in the jejunum, in the presence of a gastrocolic fistula, the gastroscope may be passed into the colon. Similarly, the coloscope may be used to view the gastric remnant from the colon. In simple stomal ulceration, if the ulcer is tucked away under the lip of the anastomosis, a side-viewing instrument may be required. The gastroscope may also be helpful in obtaining biopsies.

Where stomal ulceration or a gastrocolic fistula is suspected but not found on roentgenologic examination, endoscopy is indicated and is likely to confirm or exclude the diagnosis.

Treatment

Intravenous alimentation should be instituted promptly when the diagnosis is suspected and continued during the patient's work up. Anemia and electrolyte imbalance should be corrected. With this regime there usually is relief of symptoms and the patient's weight will generally increase. Originally, one-stage resection of the fistula was recommended, but the mortality was so high, varying from 35-63% (7), that various staged procedures were introduced. After Pfeiller and Kent (9) recommended preliminary defunctioning proximal colostomy which stopped the diarrhea, this became widely accepted until recently. Localio et al (10) noted the poor results obtained with multiple bypass techniques and with disconnection of the fistula, and advocated partial gastrectomy. Andros et al (4) also found staged procedures gave poor results, and that with improved preoperative preparation, one-stage procedures were the best. The result of this case supports the view that with adequate preparation following hyperalimentation, a one-stage procedure may be done, together with an excision of the fistula.

Discussion

The onset of significant gastrointestinal symptoms some time after surgery for peptic ulceration should call to mind recurrent or stomal ulceration; sudden exacerbation of these symptoms arouses suspicions of a gastrocolic fistula.

This case exhibited the usual symptoms, reflecting the failure of his previous medical and surgical treatment for duodenal ulceration. Investigations indicated that he had a large remaining parietal cell mass, despite his previous subtotal gastrectomy and probably an excessive neuronal response to stimulation through the vagi. His normal serum gastrin excluded the Zollinger-Ellison syndrome, gastrin-secreting adenomas, and a retained antrum, and suggested that truncal vagotomy and a reduction in the size of his parietal cell mass by resection was indicated. After appropriate preparation with total intravenous alimentation, this surgical treatment was achieved in one stage with good result.

It is interesting that on endoscopy in this case neither the afferent nor the efferent loops of jejunum appeared inflamed as expected. The large stomal ulcer made it easier to pass the scope into the colon than into the jejunum.

The use of the combined procedure of truncal vagotomy and Billroth II partial gastrectomy has resulted in marked decreased incidence of stomal ulceration and with it almost disappearance of gastrojejunocolic fistula (4).

Summary

The case of a patient with gastrojejunocolic fistula is presented and is believed to be the first recorded such case in which the fistula was visualized by gastroscope and colonoscope and treatment was by intravenous alimentation followed by one-stage vagotomy with en bloc resection.

Acknowledgment

We wish to thank Dr. J. Strauss of Mount Sinai Hospital for performing gastrin estimation.

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NEUROLOGIC-NEUROSURGICAL NOTES

JOHN LUSINS, M.D. AND MARTIN H. SAVITZ, M.D., COEDITORS

Von Hippel-Lindau's Disease: Case Report and Oncogenic Consideration

Submitted by

YONG-MYUN RHO, M.D., VED P. SACHDEV, M.D., AND
LEONARD I. MALIS, M.D.

Von Hippel-Lindau's disease is a heredofamilial disorder characterized by vascular tumors of the retina (1) and central nervous system, especially the cerebellum (2). The cerebellar lesion is usually a solitary hemangioblastoma; but in about 10 percent of patients, the neoplasms are multiple and involve the spinal cord and cerebrum (3). The regular occurrence of cysts in the pancreas and kidneys permits a classification of phacomatosis. Association with polycythemia (4) and syringomyelia (5) and pheochromocytoma (6) has also been described. The purpose of this paper is to present a well-documented case with all of these reported stigmata of this rare neurocutaneous syndrome. It is intended that this report supplement the previous publication on von Hippel-Lindau's disease by one of us (7).

Case Report

The patient was a 49-year-old woman whose history of present illness dated back 16 years when she developed progressive difficulty in walking, slurring of speech, frequent headaches, and double vision. She underwent suboccipital craniectomy twice for excision of a cerebellar hemangioblastoma and its recurrence over a ten-year period, each time with an apparently good postoperative recovery. She was able to perform her regular job as a secretary right up until her admission to Mount Sinai Hospital. On the day of admission, she experienced severely ataxic gait and debilitating cephalgia.

Significant in her medical history was infantile paralysis at 17 months of age with residual quadriparesis and kyphoscoliosis. Only partial family history (Fig. 1) could be obtained because various members were scattered. Her father died of a recurrent cerebellar hemangioblastoma which was confirmed histologically. Her mother was alive and well. Her paternal uncle also died of a brain tumor. There were six other siblings. One brother and one sister had cerebellar hemangioblastomas which were confirmed by histology. One sister had been epileptic since childhood, but never underwent diagnostic studies. One brother died in infancy and two brothers were apparently healthy.

On physical examination, the suboccipital craniectomy site was bulging and pulsating on the right side, and a loud bruit could be auscultated. Neurologic examination demonstrated ebullient speech, marked cerebellar ataxia, and a positive Romberg's sign with

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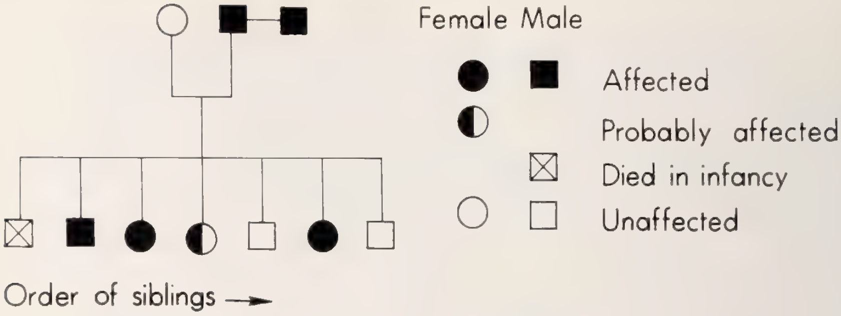

FIG. 1. Pedigree of patient.

falling toward the right. All of the muscles in both lower extremities exhibited some atrophy, but only the intrinsic muscles of the left hand were atrophied in the upper extremities. There was generalized hyporeflexia, and no pathologic reflexes were elicited.

Funduscopy revealed bilateral papilledema as well as an angiomatous lesion of the upper outer quadrant of the right retina (Fig. 2). The hemoglobin was 20.3 gm %, and the red blood count was 7.63 million/mcc. Bilateral retrograde brachial angiography showed a large, highly vascular tumor involving the posterior fossa, replacing almost entirely the right cerebellar hemisphere and extending across the midline (Fig. 3). The increased vascularity is evident from the dense tumor blush and filling of jugular vein in neck in the early arterial phase of the angiogram. The tumor stain extends well below the region of suboccipital craniectomy site. Posterior fossa is very tight with some upward herniation of posterior fossa contents.

The patient underwent suboccipital craniectomy on November 19, 1973. Surgery was carried out in sitting position using Gardner's head-pin fixation. Intraarterial catheter in radial artery provided constant blood pressure monitoring. A central venous pressure line was introduced through antecubital vein into right auricle and an anti-gravity "G" suit was wrapped around lower trunk and both lower extremities to increase venous pressure and thereby help prevent air suction from opened veins in operative field. A Doppler ultrasonic monitor was placed over precordium for early detection of even small air embolism. Operative findings included large arterial and venous channels in the muscles and scar tissue covering the area of previous surgery and in the adjacent dura mater, in addition to a large fleshy and vascular tumor filling the entire right side of posterior fossa and extending to the opposite side. During dissection of the tumor under operating microscope a large, thin-walled vascular channel in the dura mater was seen open but without any bleeding. This opening in the vessel was closed within seconds of its discovery but massive air embolism occurred very quickly as indicated by gross disturbances of Doppler rhythm and the EKG changes. Air embolism was confirmed by suction of frothy blood through CVP line as well as direct needle aspiration from right heart. Despite all resuscitative measures, the patient died of massive air embolism within minutes after the onset of embolism.

At autopsy, hemangioblastomas were found in the cerebellum, cervical spinal cord, and retina of the right eye. The spinal lesion was accompanied by a large syrinx (Fig. 4). Histologically, these tumors were composed of sheets of pale, spindiloid cells separated by thin, delicate, blood-filled sinusoids. Multiple nonvasoformative cysts were present in the pancreas, kidneys and liver. Three nonspecific leiomyomata were noted in the uterus. The right adrenal weighed 25 gm and its medulla was replaced by a dark red, moderately firm tumor, measuring approximately 5 cm in average diameter. The center of this tumor was yellowish in color, gelatinous in consistency, and about 1.5 cm in diameter. The surrounding adrenal cortex was deep yellow and well demarcated. Microscopic examination showed a large tumor that was gradually arising out of the adrenal medulla. There was no clear

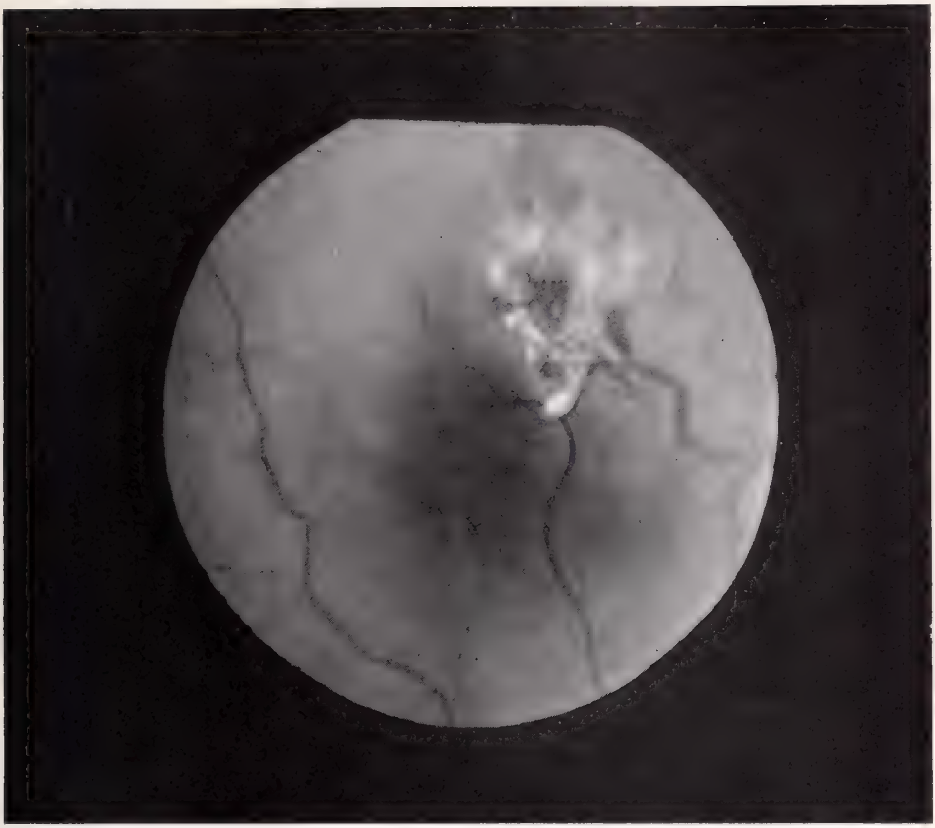

FIG. 2. Angiomatous lesion in the retina.

separation between the tumor tissue and normal parenchyma. The neoplasm was made up either of loosely arranged trabeculae of cells separated by honeycomb-like spaces or a solid mass of cells containing delicate capillary sinusoids. The tumor cells were irregular in size, but mostly ovoid or spindle-shaped, and contained clear, unstained or faintly acidophilic granular cystoplasm and large, hyperchromatic nuclei, which were often bilobulated or multilobulated. The tumor tissue fixed in solutions containing a chromate salt failed to show any chromaffin granules in the cytoplasm. Fat stains of the frozen sections revealed occasional sudanophilic granules. The stromal network was rich in elastic fibers, but only scanty in collagenous fibers. Except for the nuclear characteristics that resembled pheochromocytoma, the cellular pattern had a close morphologic resemblance to the hemangioblastomas of the central nervous system (Figs. 5 & 6).

Discussion

The mode of transmission in von Hippel-Lindau's disease is by an autosomal dominant gene (7, 8). Even the limited family history in the present case demonstrates the strong hereditary nature of this phacomatosis. Out of seven siblings, three were definite diagnoses; and at least one more was probably affected.

It has been suggested that the hemangioblastomas of the central nervous sys-

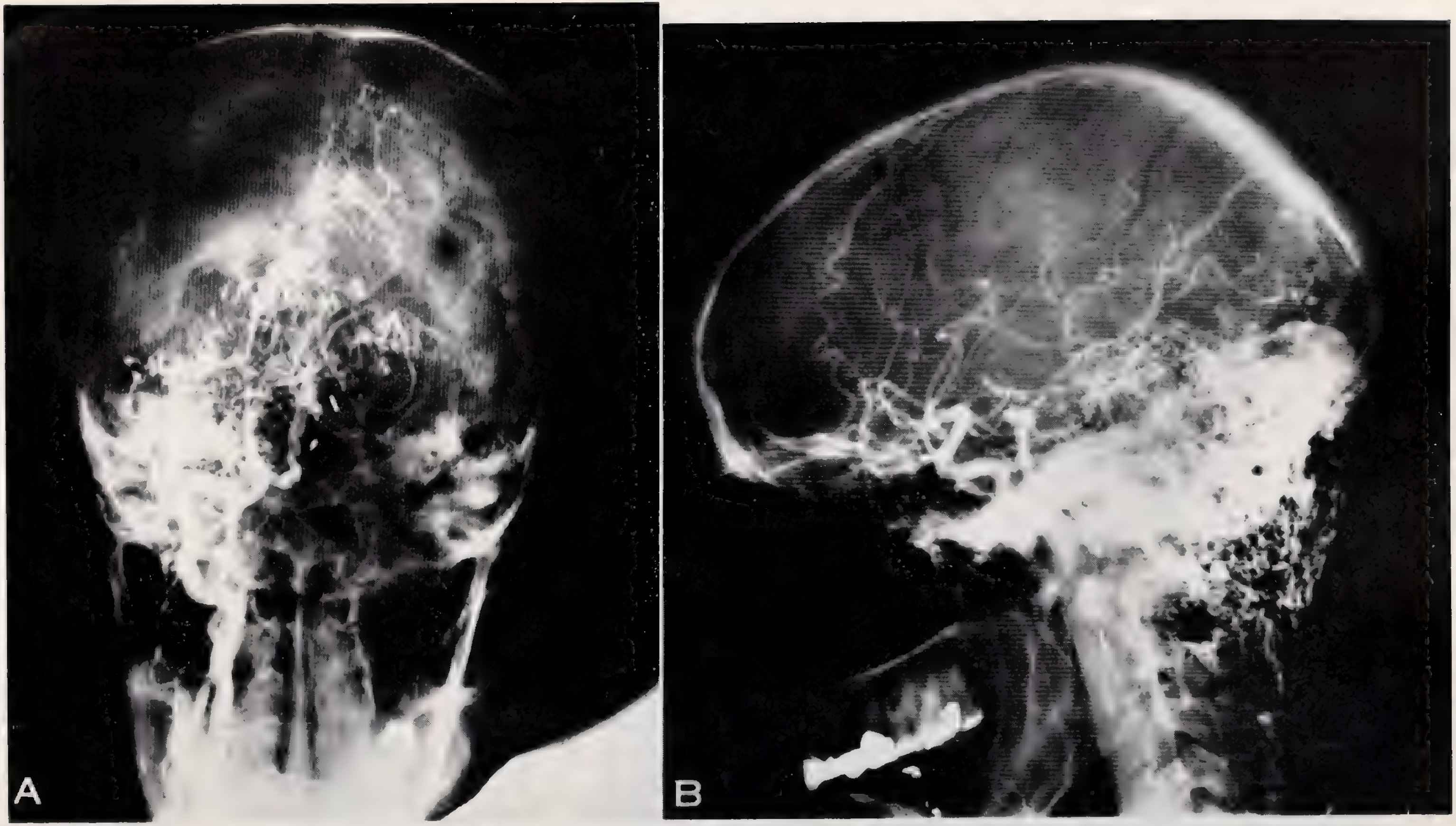

FIG. 3. Brachial angiogram showing a large, highly vascular tumor in cerebellum.

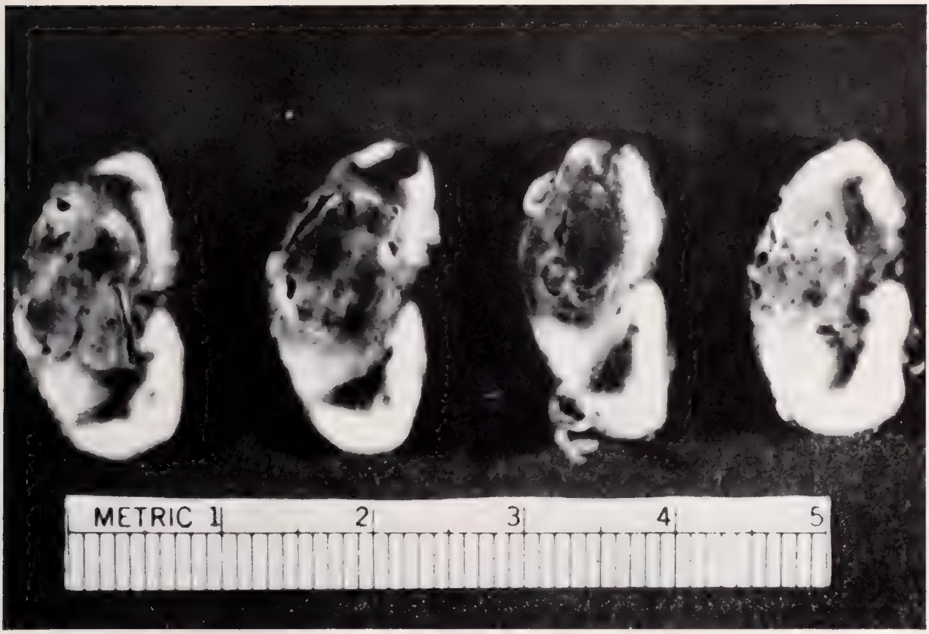

FIG. 4. Hemangioblastoma in cervical spinal cord.

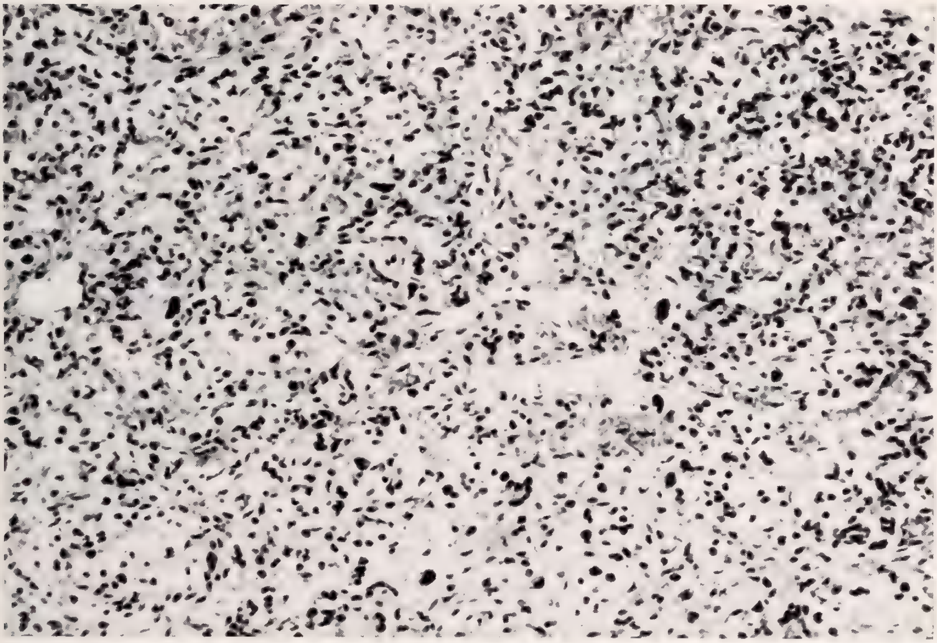

FIG. 5. Adrenal tumor composed of non-chromaffin cells arranged in angiomatoid fashion (H & E × 290).

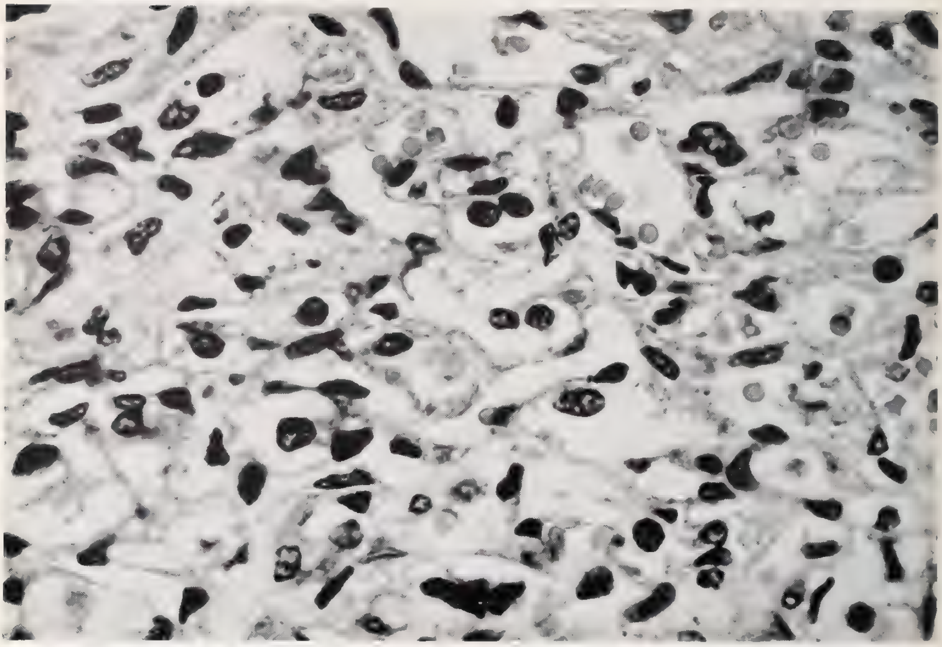

FIG. 6. Adrenal tumor composed of non-chromaffin cells arranged in angiomatoid fashion (H & E × 530).

tem and retina, pheochromocytomas of the adrenal, paragangliomas of the sympathetic chain, and hypernephromas of the kidney reported in von Hippel-Lindau's disease may have a common oncogenic factor, and that these tumorous lesions may represent divergent manifestations of the same genetic defect (8). The tumor found in the right adrenal exhibited the histologic features of both pheochromocytoma and hemangioblastoma. Zak (9) considered the cerebellar and retinal lesions as carotid-body-like structures and von Hippel-Lindau's disease as an instance of multicentric glomic neoplasia; the absence of chromaffin granules in the tumor cells of the adrenal medulla may be explained by this concept.

The treatment of cerebellar hemangioblastomas is surgical (10), but extirpation must be complete if recurrence is to be avoided (11). Optimum operative results are obtained by microneurosurgical technique. Sitting position offers the best approach to the posterior fossa. Air embolism is a serious complication in sitting position, but in a vast majority of cases the embolism can be detected early by Doppler ultrasonic monitor and corrective measures taken.

Summary

A case of von Hippel-Lindau's disease in a 49-year-old woman is presented. The diagnosis was made by multiple surgical excisions, funduscopy, cerebral angiography and family history and confirmed by postmortem examination. Oncogenic factors are discussed.

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The Student's Corner

JEFFREY BUCKNER, B.S., EDITOR

The Mount Sinai Hospital has always been a teaching hospital, but the establishmentof the Medical School brings with it special concerns and points of view. This new column is a forum for the medical student to comment on issues concerning medical school and medical education.

The editor of this column is a first-year medical student, elected student representative, and first contributor to the column. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other medical schools are also invited to contribute.

Contact Mr. Buckner through Dr. Edra Spilman's Office, The Annenberg Building, 13-98A, The Mount Sinai Hospital, Fifth Avenue and 100 Street, New York, N.Y. 10029. If you do not have time to write an entire column, you can still contact Mr. Buckner and share your thoughts on a particular subject which can perhaps be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

In biology the more different ways an observation is confirmed, the more reliable it is and the less likely it is to be an artifact. Applying this principle to the biological process of learning in the preclinical years, one would expect to find a wide variety of types of examinations, yet what one finds is that one type of exam, the short-answer, objective test, predominates. The utility of such tests in evaluating students is well established, as the MCATs and National Board exams attest. However, to rely on the same format in curricular exams, where the object is more to teach students than to evaluate them, makes little sense. Within a curriculum, the criteria for designing a good examination should be the same as for the lectures and demonstrations. The widespread adoption of pass-fail grading, especially as at Mount Sinai where passing students are identified only by code, minimizes the importance of evaluation in the early years. On the other hand, many of the examinations which students take, here and at other medical schools, are composed for the most part of multiple choice questions apparently patterned after the National Board Exam. While such examinations may measure a student's education they certainly do not contribute to it.

Consider the following example which appeared on a recent quiz: The canals of Hering are lined by a) hepatocytes; b) endothelium; c) cuboidal ductule cells; d) ductule cells on one side, hepatocytes on the other; e) hepatocytes on one side, space of Disse on the other. This question is typical in several ways. First, it has only one correct answer yet all five choices are more or less reasonable. In part this is the result of the computer program which corrects many of our exams and is set up to eliminate incorrect choices which are rarely selected or which are selected by students who do well on the exam overall, so that with each revision the questions become more exacting and less misleading. On those grounds the sample question is a good one, yet an examination consisting of many such questions is unlikely to be of much value to the person taking it. Instead, information is fragmented into isolated facts, thus favoring the straight forward acquisition of data at the expense of the relations intrinsic to the material which make learning it exciting and knowing it useful. With the present approach, examinations which could function as a kind of individual instruction are too often merely obstacles.

This is not to say that multiple choice questions are worthless for teaching. On the contrary, what they emphasize is important but unless they are accompanied by other types of questions, which require more of an answer than "a," "b," "c," "d," or "e," they waste the teaching opportunity which exams present. Exams which demanded as well that phenomena be explained and problems solved would, I think, be much better preparation than they presently are.

This proposal that exams should be aimed more toward our anticipated experience as makers of diagnoses and decisions is not a disguised request for increased clinical exposure nor is it the perhaps familiar complaint that there is too much memorization; none of us will find out about that for several years. Recognizing that facts must be acquired before they can be used, this is a proposal that our initial medical education be oriented more toward the uses of information than its acquisition.

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Editors' Note

During his long life (1898–1974) Alan F. Guttmacher was a practicing obstetrician, an academic teacher, a social reformer in the field of human reproduction, and a great educator whose voice was heard throughout the land and indeed throughout the world. To the authors who have contributed to this special issue of the Journal and to us, the editors, as well as to untold others, he also was a good friend and a magnificent human being.

To honor Alan's memory we have tried to bring together a series of papers representative of as many as possible of the several disciplines and areas of concern in which he was active. Since his range of interest was so broad it was difficult to organize the contributions in a meaningful way without splintering the whole into too many parts. We finally settled on four major sections: Population and Family Planning; Methods of Fertility Regulation; The Art and Science of Medicine; and Psychosocial Considerations. Within each section, papers are arranged alphabetically by first author.

Joseph J. Rovinsky
Christopher Tietze

This tribute to Dr. Guttmacher is being published with the support of The Guttmacher Institute, the Research and Development Division of the Planned Parenthood Federation of America.

Family Planning and Malaria Control: Some Parallels between Two Large-Scale Health-Related Programs

RICHMOND K. ANDERSON, M.D., PH.D.

The importance of the medical profession in providing contraceptive advice and services has long been recognized and has been made further apparent by recent developments in contraceptive technology. Correspondingly, countries which in recent years have developed large-scale family planning programs have usually given primary responsibility for implementing these programs to their health service organizations. Therefore, it may be interesting and perhaps helpful to review and compare family planning and other large-scale international health programs. Many parallels exist between the problems and progress of international health programs, such as those for combating smallpox, venereal disease, cholera, tuberculosis, and malnutrition, and between each of these and family planning, but because of space limitations only one will be discussed here: malaria control, which has been regarded with reason as one of the modern health miracles. In discussing family planning in the context of public health programs, it should be made clear, however, that family planning belongs within a much broader context than health alone, and the importance of involving other disciplines and agencies, both public and private, cannot be overemphasized.

Various means of avoiding pregnancy have been accepted culturally and practiced for thousands of years in the so-called developing countries, but it was hardly more than a decade ago that some of these countries became sufficiently concerned with the effects of rapid population growth to implement large-scale family planning programs. While India and Pakistan, in 1952 and 1960 respectively, adopted family planning as national policies, programs existed largely on paper until 1965 when both were reorganized. Several other countries also encouraged family planning,* either officially, such as Korea in 1961 or largely as private activities, such as Hong Kong in the late 50's and Fiji and Taiwan in the early 60's. However, programs on any relatively large scale date from the latter part of 1964 when the IUD began to be widely available, and it was not until a

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* In the People's Republic of China statements favoring family planning were made as early as 1956, but the official view in the late 50's and early 60's seemed to be that a big population was a good thing. A "second" birth control campaign is said to have begun in 1962 but was neglected during the "cultural revolution." Apparently the program was reactivated in 1969 and was given high priority in 1971 (1). Other programs approved relatively early were in Tunisia in 1964, and Egypt, Mauritius, Turkey, Ceylon (now Sri Lanka), and Singapore in 1965.

year or two later that the commercial price of oral contraceptives permitted their widespread use in programs in developing countries.

The ensuing decade has seen the acceptance in principle of responsibility for providing family planning services by governments representing over 90% of the population of the developing world, either for the purpose of reducing rates of population growth (governments of countries representing about 75% of the population) or on a health and/or human rights basis (2). All but two (Burma and Ethiopia) of the countries with over 25 million population now have official policies of providing family planning services. Furthermore, about 60% of the world's population now live in countries where abortion for other than medical reasons has been legalized. This rapid spread of interest in and acceptance of family planning is especially impressive when one considers its political and personal sensitivities and profound sociocultural implications. Compared with the early expansion of other health-related programs, this is almost unprecedented.

But what of the progress and actual and potential effectiveness of these family planning programs? Opinions vary from "the population crisis . . . will be largely . . . a matter of history when humanity moves into the 21st century"(3), "evidence is emerging that fertility rates are declining in many countries, both rich and poor, on every continent" (4), and "where services were made readily available . . . in developing countries, the most effective methods were adopted, fertility declined . . . the number of unwanted births dropped and lower birth rates resulted" (5) to "disappointment at the results of the family planning approach" (6) and "the stark truth is that family planning programs have been a dismal failure" (7). Obviously these marked differences reflect the judgments of individuals, based on their estimates of past and potential future progress. Such judgments should take into account the following:

1. How difficult is the implementation of such programs? Any program which requires a change in long-established attitudes, motivations, and practices is extraordinarily difficult, but none more so than one involving changes in sexual behavior and in attitudes involving pride in, love for, and dependence on children and the family, especially in societies which traditionally are high fertility-oriented. Furthermore, implementing such programs in developing countries involves enormous logistic and technologic problems.

2. Has there been sufficient time for programs of such difficulty and complexity to achieve the desired results? A decade is a very short time for such programs to become well-organized in a multiplicity of countries and political situations, and even after a vigorous program has been organized, one should not expect a measurable impact on fertility before a minimum of about five years (4).

3. Have the financial and political inputs been sufficient to encourage, implement, and support an effective program? In general, budgets have been low, particularly so for governments that regard their population situations as serious. Typically, the reported investment in family planning varies from

0.01–0.20% of the national budget, with a few, for example Fiji and Jamaica, having risen to 0.30–0.40%. Indonesia and India recently have been spending in the range of 1% (which includes major foreign contributions) and 3–4% respectively (2), but in both countries a large share of the family planning budget is being invested in development of their health infrastructures.

In regard to international funding, the World Bank allegedly has earmarked about 1% of its funds for population programs, the US puts about 5% of its foreign aid into population activities, and among other governments which provide international assistance, the average allocation for population is only about 2.3% of their total aid (8).

In many countries, the health ministry is one of the weakest and least prestigious. Other ministries, stronger politically and financially, often seem glad to wash their hands of involvement in this sensitive, difficult, and politically unrewarding activity. Some components of family planning programs are better undertaken by ministries other than health. If so-called "beyond family planning" methods (9) are to be utilized, most of these must be primarily the responsibility of other ministries.

4. What are the criteria for success of a program? There have been relatively sharp to moderate declines in birth rates in countries such as Taiwan, South Korea, Hong Kong, Singapore, Malaysia, Sri Lanka, Egypt, Tunisia, Mauritius, Cuba, Chile, Costa Rica, Jamaica, Barbados, Trinidad-Tobago, Puerto Rico, and Fiji, and probable declines elsewhere, especially in the Central America/West Indies region (4, 10); and at least programmatically there appear to be encouraging trends in countries such as Indonesia, the Philippines, Thailand and Colombia. Reports from the People's Republic of China certainly give the impression that its family planning program, apparently aided by considerable input of so-called "beyond family planning" activities, is effective (11). In some countries the evidence seems to indicate that "the program"* was responsible for a substantial part, though certainly not all of the decline, while in others the effect of the program is uncertain. There does appear to be some correlation between the declines in birth rates and the level of programmatic activity (4, 10).

Considering India's enormous logistic and other problems, even its progress appears somewhat encouraging, especially to one who remembers a time when expressing a view favorable to family planning brought accusations of immorality, atheism, and hatred of Indians. India illustrates a very understandable propensity to judge a family planning program not in terms of whether some progress is being made but rather against its present capacity to solve a near or actual crisis situation. The seriousness of the world's population problems hardly can be overemphasized, but should family planning programs (which regardless of other developments and inputs will be needed as a means of limiting births) receive any less priority at a time when they appear to be achieving significant results, even though they clearly are not now solving, and without additional supportive measures are probably incapable of solving, these serious and difficult problems?

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* What is or is not a part of "the program" often cannot and probably should not be defined very rigidly, since important influences and activities may result even though not directly promoted or administered through the program: for example, creating a climate favorable to family planning, encouraging the private distribution of contraceptives and services, etc.

There has recently been increasing emphasis on economic and social development as an indirect but presumably necessary and more promising approach to reducing population growth. Development has been the major thrust of most foreign assistance programs for the past quarter century (12). Yet it is generally admitted that the spread between the economies of the developing and developed countries is *increasing* rather than *decreasing*, and populations are burgeoning. Does this mean that development programs have failed and should be cut off? A more valid conclusion would be that both economic and social development and family planning programs (which are also a part of development) need greater emphasis, along with other inputs, eventually probably including some that are not yet acceptable politically.

Malaria control programs have a much longer history (13–15) than those in family planning, and in general have achieved a higher degree of success and of public and political acceptance. Nevertheless, malaria programs over the years have been beset with similar problems of inadequate financial and public support, of overly optimistic expectations of early success, of varying judgments of their actual and potential achievements, of controversy over whether malaria was primarily a social or a medical problem, and correspondingly whether control should be promoted primarily through socioeconomic development or through public health measures, and especially by the myriad of political, administrative, logistic, financial, and cultural factors associated with the implementation of new activities in developing areas.

Malaria had been common throughout much of the world from time immemorial. During the 17th through 19th centuries, it was prevalent in the US from New England to Florida and extended westward with the settlement of the country. It was estimated that there were still over a million cases yearly as recently as 1920, and nearly a half million in 1940. A leading public health text published in the U.S. in 1941 (16) states that "a large proportion of the population does not believe as yet that malaria is transmitted by mosquitos."

It has long been recognized that malaria was associated with "bad air" (hence the name "malaria"), especially air rising from swamps (hence the Spanish name "paludismo" from palude—a swamp). Starting in the early 18th century, there was increasing suspicion that mosquitos were in some way involved. In 1880, the French army surgeon, Laveran, clearly described the malaria parasite. In India in 1897, Sir Ronald Ross identified the malaria parasite in anopheles mosquitos. In 1898 he was able to demonstrate the transmission of bird malaria by mosquitos, and a group of Italians promptly proved that mosquitos were also the vector for human malaria. In 1900, Manson demonstrated that malaria, even in highly malarious areas, could be prevented by screening of living quarters.

However, effective therapy and methods of prevention considerably antedated the discovery of the cause of malaria. In the first century A.D., the Roman emperor Nerva was praised because his drains removed the causes of "bad air" and improved Roman health. The first recorded use of cinchona bark or "fever tree bark" was in Peru in 1600. Quinine was used successfully as a prophylactic among railroad workers in the United States as early as 1844. In 1793 whale oil, in 1892 petroleum oil, in 1916 Paris green, and in 1918 pyrethrum were used as mosquito larvicides.

By the turn of the century, the cause and mode of transmission of malaria were established, an effective drug for treatment was known, and good preventive measures were available, including drainage, screening, and larviciding, a combination of knowledge and technology probably at least as effective as that available for family planning today.

Several spectacular successes followed. Gorgas practically eliminated both yellow fever and malaria from Havana in 1908, and from the Canal Zone between 1904 and 1914. The United States Public Health Service became involved in malaria control in 1912–13; and the Rockefeller Foundation became involved in it in 1915. Malaria control spread gradually from America and Europe into other parts of the world and was incorporated into many health services.

In 1924, the Malaria Commission of the League of Nations issued its first report. In spite of the successes in malaria control, it noted a lack of correlation between malaria and anopheles mosquito distribution and said: "If permanent results were to be desired, a very complicated program would have to be realized. Local conditions would have to be improved, . . ." In its second report the Commission stated: "The history of special antimalarial campaigns is chiefly a record of exaggerated expectations followed sooner or later by disappointment . . . This record of failure and disappointed hopes makes it clear that the only prospect of real progress lies in renewed activity in the continuous study of the disease in all its aspects." How familiar these quotations become if one substitutes "family planning" for "antimalarial" and "population" for "disease"!

In 1927, the Malaria Commission sent two experienced malariologists to the United States who reported in substance that malaria in the U.S. was decreasing at a constant rate, a course that had begun, like that of other *social* ailments, before action had been taken against it, and that it was gradually disappearing for reasons connected rather with social and economic progress than in consequence of preventive health measures; again a currently familiar type of statement if one substitutes "excessive population growth" for "malaria".

Opinions in Europe began to crystallize against spending large sums of money on attacking the anopheles mosquito. In 1927, the Malaria Commission, which included no one who had had much success in controlling malaria by antimosquito measures but was, nevertheless, a notable group of experts in *other* aspects of malariology, reported as follows: "When the discovery of the mosquito cycle of the parasite was made, it was almost universally believed that a single method had been put into our grasp capable of application in all malarious districts. Since then nearly three decades have passed and such a method is still to seek" —a statement akin to current deprecation of the potential effect of new contraceptive techniques on population growth.

In 1929, a respected scientist, S. P. James (17), advisor on tropical disease to the Ministry of Health in England, emphasized the lack of correlation between malaria and anopheles density* and the failure of control with so-called U.S. methods in some areas. He wrote: "It is surprising that a section of the older school of malariologists still pin their faith to anopheles reduction as the best method of controlling malaria . . . malaria like tuberculosis and syphilis is a *social* disease . . . economic improvement is the matter to which attention must first be paid." His statements are reminiscent of those who believe that social and economic change is the best approach to reducing rates of population growth.

Thus three schools of thought were developing: (1) those who would rely chiefly on prevention through mosquito control (primarily by drainage and larviciding); (2) those who recommended treatment with drugs (largely quinine); and (3) those who felt that there was no effective recourse except through further research and through social and economic change. These polarizations of opinion are not dissimilar from those who in family planning would concentrate (1) on prevention through contraception; (2) on treatment through abortion, or (3) on economic and social change.

Other important developments were also taking place. Better antimalarial drugs were synthesized. In 1930, a notoriously effective transmitter of malaria, Anopheles gambiae, was introduced into Brazil from Africa and in 1938 caused what was probably the most explosive epidemic ever seen in the Americas. An anti-gambiae program, set up by the Brazilian Government in cooperation with the Rockefeller Foundation, completely eradicated the Anopheles gambiae mosquito from Brazil in 1942, establishing a new landmark of "species eradication" in malaria control.

Meanwhile malaria was gradually subsiding in the United States. Why it eventually retreated so completely has been the subject of much speculation. Control measures which included screening, quinine prophylaxis, drainage, and larviciding, were begun in some areas about the turn of the century, and the U.S. Public Health Service and the Rockefeller Foundation started malaria demonstration projects in 1912 14. The establishment of the TVA brought malaria control to an area of five southern states.

Before and during the early years of World War II, malaria was still endemic in some parts of the South,† leading to the establishment of MCWA (Malaria Control in War Areas) with headquarters in Atlanta, (later reorganized into the Communicable Disease Center). By the end of the war, malaria was almost eliminated from the United States.

There were, however, other very important factors in this decline, such as land improvement, drainage for agricultural and other purposes, general and public health education, increase in farm animals which mosquitos might bite instead of humans, better housing with widespread screening, population shifts from malarious to nonmalarious areas, and urbanization. These social and economic factors were perhaps equally or more important than the malaria control programs, though without them progress certainly would have been very much slower.

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* Lack of correlation was later shown to be due to minor differences between the local vector and other mosquitos of the same species, distinguishable only by minor differences in their eggs, to differences in their habits of biting man vs. animals, etc. (13).

† The author worked in rural North Carolina in 1942–43. At that time malaria was the most common clinical diagnosis made for a mild fever by doctors in the area. Since a blood smear survey indicated that malaria infection was rare, this diagnosis was obviously a holdover from earlier years when malaria was much more common.

Though DDT was synthesized in 1874, its insecticidal properties were first noted in 1939. Widespread use of DDT and other residual insecticides followed. Its successful use in Italy lead to a national program which eradicated malaria from that country in five years. Venezuela, beginning in 1945, was the first to attempt a nationwide eradication program. Ceylon, after a major malaria epidemic in 1946–47, implemented a successful control effort to which some have attributed, though on controversial evidence, the accompanying marked increase in the rate of population growth. Several province-wide programs were implemented in India beginning in 1948, and others followed in Asia, Africa and Latin America.

About 1951, however, it began to be noted that anopheles, in addition to other mosquitos, were developing resistance to the insecticides. Resistance of the malaria parasite to some of the antimalarial drugs was also observed. Problems of human resistance also arose. Initially the householders were enthusiastic over the way spraying controlled malaria and killed mosquitos and other insects, but pest mosquitos and the other insects became resistant more quickly than the anopheles, whose bite is comparatively less irritating. With the threat of malaria subsiding and the mosquito nuisance returning, the spraying teams became less and less welcome. Some malariologists, therefore, felt that it was necessary to eliminate malaria before insect and parasite resistance and human indifference developed further.

The Pan American Sanitary Conference in 1954 called for malaria eradication as contrasted to malaria control, and in 1955 the World Health Assembly recommended that WHO take the initiative in developing worldwide malaria eradication programs. UNICEF came up with immediate financial aid and the Congress of the United States offered assistance.

Malaria eradication programs spread rapidly to many of the malarious areas of the world, serving to help control malaria in many places and make progress toward eradication in some. Gains were recorded in many countries but massive reverses occurred in Ceylon and India in 1968, eradication was found not to be feasible in a considerable number of countries, and the core of endemic malaria in the tropics of Africa, Asia, and Latin America persisted. WHO reports emphasized that, although there were important technical problems, these were relatively minor as compared with all the administrative, logistic, financial, political, social, and cultural factors which impede new activities in developing countries.

That the malaria situation has improved in many parts of the world is evident to anyone who traveled widely before and after these massive campaigns were started, but travelers are still at risk of contracting malaria in most developing areas of the world. A recent WHO bulletin (18) indicates that risk exists in nearly all tropical areas of continental Africa, in most of Central America, in tropical Latin America, most of Southeast Asia, and in the Western Pacific.

A look at areas which are no longer malarious is revealing. Aside from some 40 countries where malaria did not exist or had disappeared for causes other than malaria control programs (mostly countries in Europe or Oceania), countries where malaria eradication has been "registered" by WHO include Mauritius (the only "African" country), most of the West Indian islands, the United States and Puerto Rico, Bulgaria, Cuba, Cyprus, Hungary, Italy, the Netherlands, Poland, Portugal, Romania, Spain, Taiwan, and a part of Venezuela. In addition, in nearly all of Europe and Oceania plus a number of countries such as Israel, Lebanon, Japan, Chile and Uruguay, travelers are claimed to be free of risk.

This is a considerable success but it is obvious that with very few exceptions all of these represent special situations in developed countries, islands, or relatively small areas. Thus, it could be claimed for malaria eradication, as it has for family planning, that success has not yet been achieved in any of the *large* less developed countries; and the correlation between the areas where malaria persists and fertility and population growth rates remain high is surprisingly close. Does this mean that efforts at malaria control and eradication should be cut back and reliance placed on economic and social development which clearly has been an important factor in the retreat of malaria in many areas? The benefits of malaria programs have been too great to consider such a course, but further economic development and improvement of environmental and living conditions will very likely be necessary for eventual eradication.

Experience with large-scale health-related programs such as malaria control and family planning point toward the following conclusions:

1. It is unrealistic to expect prompt acceptance and rapid success of large-scale health-related and other programs which require revision of deep-seated cultural attitudes, depend in considerable part on socioeconomic change, and are logistically very difficult to organize, implement and administer in developing countries.*

2. Good technology is important if not essential for a successful program, but much more than good technology is necessary.† An effective system of bringing services to the people, not easily achieved in developing countries, also needs to be organized, both to take advantage of present technology and of even better technology when it becomes available.

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* Similar parallels could be drawn with other than health-related programs. For example, although the basic research leading to hybrid corn was done in the first decade of this century and hybrid corn seed became commercially available in the mid-1920's, even in the U.S. only some 23% of corn acreage was planted to hybrid corn by 1939, and not until 1959 did the total acreage so planted reach 95%. About 1943, the Rockefeller Foundation began to lay the foundations of the "Green Revolution" by developing in Mexico improved strains of corn and wheat and later of other food crops for use in tropical climates. However, it was about 25 years before the Green Revolution made a significant impact on world agriculture.

† The author recalls a time when some in India said that its population problem could largely be solved if only an effective daily contraceptive pill were available. The "pill" has now been widely available for about a decade but is not yet readily obtainable through India's family planning program!

3. Good technology plus accessibility to services are insufficient without widespread public acceptance. A sizable and growing number of people appear to want family planning, many of them lack adequate services, and making these services readily available warrants the highest priority. However, the general level of motivation will have to be raised in developing countries if the needed reductions in birth rates are to be achieved. This will require a gradual process of public information and education, of change in attitudes toward reproductive behavior, and of social and economic development.

4. Changes in response to a large-scale health-related program should not be expected to take place quickly. However family planning programs appear to be having an impact and, in combination with other measures, may well enable developing countries to lower birth rates more quickly than in the past (19).

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Population Growth and the Quality of Life

ALLAN C. BARNES, M.D.

Difficult as this topic may be to conceptualize, almost defying precise analysis, nevertheless it is a fitting subject for consideration in a volume memorializing Alan Guttmacher. He was aware of the threat of unchecked population growth earlier than many others and was always sensitive to the quality of life, both for his patients and for all humanity.

The hypothesis is advanced that at the present rate of population growth, at some time between today and the final apocalypse, we may pass a limit at which life loses its worth and value. Man is such an adaptable organism he physically may survive the worst of cataclysms, but it is also possible that he may come to a time when he no longer *wants* to survive. From sheer crowding or from increasing noise and pollution, from disappearing resources or declining food supplies, life may lose its attractiveness and zest. Is there such a deadline, and how far away is it?

Concern with the population problem stems indeed from a concern for a better satisfaction of human wants. However, population growth results from such a myriad of personal decisions that a single individual sometimes feels trapped by its immensity and unable to deflect its course. Paul Demeny (1) has summarized it thus:

> In demographic as in other matters, individuals can be trusted to pursue their own interests and satisfactions as best as their circumstances permit. But the ability of any individual to secure for himself behavior by others that is most suited to his welfare is severely limited.
>
> The problem is best seen as one of market failure. As Adam Smith observed, it is not from the benevolence of the baker that we expect our daily bread but from the baker's regard to his own interest. In acquiring what we need from the baker, we address ourselves not to his humanity but to his self-love. This classic mechanism of eliciting actions that satisfy our wants, however, cannot work when appropriate markets do not exist. Where does a citizen go to "purchase" a future in which his grandchildren will live in a US of 300 million rather than 400 million?

"The Quality of Life" is an expression heard with greater and greater frequency and has become somewhat the ultimate shibboleth among our social planners and legislators. The increased frequency with which we hear the expression reflects the apprehension with which we face our national and global future. Increasing use of the term, however, has led to increased study, and social scientists, psychologists, and behavioral scientists have made an effort to give the term more definite substance and more precise content. Not only has the phrase been analyzed as it might apply to individuals, but political policymakers have developed social indicators of national well being (2).

Interestingly, such intersocietal studies have indicated that these social concerns are surprisingly universal in nature (3). Weightings and priorities differ

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among different countries (and might well differ with time in any one country), but in general most groups have the same objectives and the same national aspirations.

It might be well therefore to examine a representative group of these social indicators. Such a list might include (3): 1) health and nutrition; 2) education; 3) income and consumption; 4) employment; 5) nonhuman productive resources; 6) housing, utilities and the environment; 7) public safety and justice; 8) political freedom; and 9) social mobility.

The attributes of leisure or of cultural heritage are omitted from such a list because they are more meaningful to people in the affluent societies and do not apply as broadly on a global basis (4). Given the presence of the social indicators selected, it is probable that most people would consider life agreeable and even self-fulfilling.

We must determine if rapid population growth hampers the achievements of each of these goals and hence diminishes the national sense of wellbeing or the individual feeling of happiness. Actually, such goals are the objectives of national development plans and their intermittent measurement serves as an index of the progress of such programs.

1. Health and nutrition. Wray (5) has reviewed the relationship between population growth and health, although his figures apply chiefly to family size (and, hence, child-spacing) more than to the total growth of the community. Nevertheless, if the number of purveyors of health care, the number of hospital beds, or the number of clinic facilities are taken as indices, it is evident that in many parts of the globe these cannot keep pace with population growth. Thus, the population doubling time for most of the countries in Central America is in the neighorhood of 22 years, without any significant hope that hospital facilities can double in this same length of time.

From the point of malnutrition, it is probable that the food-population equation is permanently dislocated (6). This is not entirely a function of population size, since maldistribution of foods, waste in the developed countries, and failures of national nutrition programs in the less developed countries influence the situation. With the North American continent the principal and almost the only exporter of grain, the precariousness of the global situation stems from the fact that much of the world is now dependent on a single weather system. Pockets of malnutrition, possibly very large pockets, are going to continue to exist, and, with most of the grain reserves now depleted, hunger and starvation will become more commonplace.

While it is an oversimplification to imagine that population growth is the exclusive cause of the situation, it is true that continuing population escalation makes the solution of the malnutrition problem more difficult. Certainly large segments of the world population are going to see the quality of their lives seriously deteriorate as food shortages recur and become more pressing.

2. Education. The desire for greater and easier access to training and education is universal, but schoolrooms cannot be doubled as fast as populations are doubling without undue expenditure of the gross national product and the national effort. New technologies for education undoubtedly will be devised, but their effectiveness and acceptability have yet to be determined. A slowing or a reversal of the rate of growth would contribute enormously to the solution of this deficiency, although it would not by itself represent the solution.

3. Income and consumption. Freedom from poverty, a sufficient income for the most basic family needs, and a protection against the eroding impact of inflation are national objectives, the achievement of which is seriously impeded by a mushrooming population growth. While the average citizens may not perceive the relationship between the increasing numbers of people who must divide up the gross national product, all of them are acutely aware of the decline in their personal spendable incomes. Personal satisfaction cannot persist long under these circumstances. Once again, population growth is a contributing cause rather than *the* cause.

4. Employment. An in-house memorandum at the Rockefeller Foundation in 1971 predicted that unemployment would become *the* global problem of the 1970's, and subsequent experience has proven this to be correct. The proximate cause of the unemployment of the 1970's is the high birthrate of the 1950's, and while many other factors pertain, such as urbanization and mechanization of both farm and industry, continuing population growth compounds the problem. In this country alone, 1.5 million people are being added every year (excess of births over deaths, plus immigration), demanding that more than one million new job slots will have to be found annually. Unemployment not only imposes serious financial problems but strikes at the sense of worth that is an essential component of the quality of life for many people.

5. Non-human productive resources. A basic social concern is that natural resources be fruitfully exploited to the benefit of all and, in so far as possible, conserved for future generations. Implicit in the phrase "nonrenewable resources" is the acknowledgment that ultimately these must be exhausted; an expanding population speeds the rate of this exhaustion. Barring the development of new and improved technology, one must anticipate a period of shortages which will change the nature of our national life and produce chronic social strain.

6. Housing, utilities, and the environment. The city of Cali, Colombia, currently has a doubling time of 12½ years (from one million people to two million) with no hope whatever that proper housing can keep pace. Sanitation and the appropriate disposal of waste are social services that also are seriously strained by soaring population figures.

7. Public safety and justice. A loss of the sense of personal safety is one of the more conspicuous phenomena of our urban centers during the past two decades. It is difficult, however, to equate this entirely with population growth.

Presumably if the number of criminals in the population remained a constant percentage, then the crimes per potential victim would not increase significantly with population growth. However, if the age group of the criminals (overwhelmingly under 25) increases more rapidly than the age group of the victims (overwhelmingly over 25), then the changing shape of our age pyramid could contribute to an increase in such crime.

8. Political freedom. A representative government with participation of all citizens and with freedom of political dissent is a social concern basic to most societies. While such a pattern currently is threatened in many areas of the world, the threat largely is from economic forces rather than simply population growth.

9. Social mobility. Mobility in this sense is not geographic as much as occupational. The freedom to change jobs and to rise to a better position is a social desideratum common to many societies.

Not one of these social indices can be related in a direct fashion to the numbers of people on the globe. Yet intuitively one views the future of a world which is adding 80 million people annually with some apprehension. In a society with maldistribution of income, pockets of severe malnutrition, with pollution increasing disproportionately to population growth, it is simplistic to maintain that zero population growth alone will "make life worth living." But continuing population escalation makes the solution of these problems and many others significantly harder. Dense urbanization, poverty, and chronic unemployment will continue for decades even if population stabilization were achieved tomorrow. Urbanization and density of population concentration may represent a greater threat than merely the numbers of people that are involved. Using medical rather than social indices, it is safe to predict an increase in the suicide rate and in the rate of psychoneurotic disturbances as more and more people concentrate in the megalopolis. In *The Death of Tomorrow* (7), Dr. John Loraine writes, "Those of brittle and dependent personality will suffer the most. The strong and self-reliant will be less affected. Feelings of loneliness and isolation will be prominent; many will feel a sense of insecurity and will complain that they are isolated from the mainstream of life. Children will be handicapped because of restricted play facilities . . . ."

Urban density itself, at least in part, is a manifestation of overbreeding. The farmer who owns a farm large enough to support one family and sires five sons is forcing four of them to migrate to the city. With severe overcrowding, it is inevitable that many of the facilities we currently enjoy will decline and that different social regulations will have to be adopted. The nature of such regulations is not difficult to visualize: by and large and of necessity they will be restrictive in form. We will find them repressive to our personal liberties as we have defined our personal liberties in the past. Men and women undoubtedly can be educated to accept these changes; but it is doubtful that mankind can achieve its fullest potential under such conditions.

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On Family Planning Associations and Development of Population Policy and Programs*

LESLIE CORSA, M.D., M.P.H.

Few persons have understood and used the power of private family planning associations to guide public population policy and programs as well and wisely as did Alan F. Guttmacher. This is an appropriate occasion to examine how family planning associations (FPA's) have affected policy and program development and, in turn, some of the effects of governmental programs upon private associations.

Students of population policy development generally are aware that most private family planning associations preceded and were active in promoting governmental programs. Quantitative estimates of the relative effect of family planning associations on government actions must await much more thorough documentation than now exists of who made major population policy and program decisions in each country, the processes by which those decisions were made, and the totality of persons and events that influenced them. A typical pattern emerges from available annual and special reports and papers of family planning associations and of observers.

A group of elite citizens, usually prominent women and physicians, become concerned about the adverse effects on the health of mothers of continued childbearing as a result of the inability of families to obtain information and means of birth control. They believe in family planning and equality for women as basic human rights. They establish a private family planning association, often local at first, which becomes affiliated with, and may have been initially facilitated by, the International Planned Parenthood Association (IPPF). This private organization, financed by voluntary contributions, plus a sizable mix of government and IPPF funds, begins to provide family planning services with its own volunteer and professional staff in its own facilities and in government and private hospitals and health centers. It operates in metropolitan areas at first, and conducts a limited educational campaign through talks, pamphlets, and local mass media. These services are utilized by women of average means and are gradually expanded to keep up with increasing demand. The need and the favorable public response are pointed out to political, civic, religious, and other national leaders, often by their wives or doctors who are themselves leaders of the family planning association.

Their efforts are enhanced in their own countries by concurrent inputs from

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demographers documenting from census data the rise in population growth rates nationally and in concentrated form in the cities, from national planners observing the detrimental effects of population growth on achievement of all per capita development goals, and from medical associations and medical educators alarmed by epidemic proportions of illegal abortions killing women and overloading already crowded hospitals. In different ways and at different times, the government responds to these stimuli by initiating and gradually increasing support of family planning services, educational activities, and other measures to prevent unwanted births, whether or not control of population growth for the common good is an overt goal.

During this same period, their efforts also are being reinforced worldwide by the work of international agencies, notably IPPF. IPPF was established in Bombay in 1952 with eight national associations as members. Its remarkable history has recently been documented (2). Without it, some countries would probably not yet have private family planning associations, and associations in other countries would not have grown so well or in some cases survived.

How can one assess IPPF's direct and indirect contributions to the many changes that occurred in government family planning policies and programs in recent years? How important in making family planning socially legitimate were the major IPPF world conferences and their widely circulated published proceedings, as well as in Stockholm (1953), Tokyo (1955), New Delhi (1959), Singapore (1963), Santiago (1967) and London-Brighton (1973); and the many IPPF international regional conferences in cities of every continent? How many leaders first became aware of the extent of population problems and family planning through attendance at such meetings, or gained strength from learning what people in many lands were thinking and doing? How much effect had IPPF's worldwide dissemination of information about new developments, establishment of standards of contraception and clinical care, and distribution of contraceptives and money from private and public sources in the MDC's to the LDC's? All of these factors did facilitate change in many reinforcing ways.

What effect have national family planning associations had upon population policy and program development of their own countries? The process remains shrouded in the mystery of unrevealed meetings, committee discussions, and personal persuasion. Family planning associations certainly are not an essential ingredient, since of the 60 countries plus Hong Kong and Puerto Rico that now have government programs (Table I), ten have no private FPA's and six established such associations at the same time as the government program or up to six years *later*. It might be taken for granted that countries with high degrees of governmental control over social and economic matters and Marxist views against birth control are not fertile areas for establishing private harbingers of new governmental activities. Yet Poland (1957), East Germany (1965), and Yugoslavia (1966) have FPA's.

The remaining 46 countries with government programs did have private FPA's before the government acted and generally followed the typical pattern above. Four are atypical in that they were the pioneers (Netherlands—1881; United

TABLE I

Initiation of Private Family Planning Associations and of National Family Planning Programs

Country	Family Planning Association Established 19—	Government Family Planning Services Initiated 19	Years between Start of FPA and of Gov't. FP Services
Afghanistan	68	71?	3
Bangladesh	53	60	7
Barbados	55	67	12
Botswana	–	72	
Bulgaria	—	*	—
Canada	63	70**	7
Chile	63	66	3
China PR	—	57/62	
Colombia	65	67	2
Costa Rica	66	68	2
Cuba	-	*	
Czechoslovakia	–	*	
Denmark	55	*	—
Dominican Rep.	66	68?	2
Ecuador	66	69?	3
Egypt	53	66	13
El Salvador	63	68	5
Finland	41	*	—
France	56	74	18
Germany DR (East)	64	*	—
Germany FR (West)	52	*	—
Ghana	67	70	3
Guatemala	62	69	7
Haiti	—	68?	—
Honduras	61	66	5
Hong Kong	50	73	23
Hungary	—	*	–
India	49	52**	3
Indonesia	57	68	11
Iran	58	67	9
Jamaica	57	67?	10
Japan	54	48	−6
Kenya	61	67	6
Korea R (South)	61	61	0
Malaysia	58	67	9
Mauritius	57	72	15
Mexico	65	73	8
Morocco	70	66	−4
Nepal	58	66	8
Netherlands	1881	71	90!
Nicaragua	70	67	−3
Norway	69	*	
Pakistan	53	60	7
Panama	66	69	3
Philippines	65	70	5
Poland	57	*	—
Puerto Rico	54	67	13
Romania	—	*	—
Singapore	49	66	17
Sri Lanka	53	67	14
Sweden	33	45?	12?
Taiwan (China R)	54	64	10
Thailand	55	67	12
Trinidad & Tobago	61	67	6
Tunisia	68	66	−2
Turkey	63	65	2
UK	30	67	37
USA	17	66**	49
USSR	—	*	—
Vietnam DR (North)	—	*	
Vietnam R (South)	68	68	0
Yugoslavia	66	*	—

* Countries where family planning services are provided as part of national health services but for which data are not available.

** Date of initial national policy or funds for family planning. States constitutionally responsible for family planning—first government service in Canada in Ontario (1967), in India in Mysore (1930), in US in North Carolina (1937).

States—1917; United Kingdom—1930; and Sweden—1933) who were motivated primarily by concern for women's rights. They engaged in sustained confrontations and legal battles over many years that greatly facilitated the work of those who followed in other countries after mid-century. In the remaining 42 countries, FPA's were established at a fairly steady rate of one to four per year from 1949 to 1969, 17 in more developed countries (1970 per capita income over $600) and 25 in less developed countries. An additional 30 or more FPA's have also been established during the same period in countries whose governments do not yet provide family planning services, although most of them can be expected to in the future.

Of the 42 (in addition to the four pioneers) whose objectives and efforts included and succeeded in convincing their governments to provide family planning services, seven provide those services as part of national health services with no identifiable date when government services began. The remaining 35 have intervals between initiation of FPA and initiation of government service of from 2 to 23 years, with a median of about 7. The intervals have been growing shorter the later the FPA was established, presumably because as more governments have programs and find them beneficial, the smaller the risks and greater the gains seen by the other governments being urged by their citizens to do likewise.

Most of the effects of private FPA's on government policies and programs can be viewed essentially as speeding up a trend whose time had come as the result of numerous interrelated changes in way of life. Examples abound in various published reports of specific actions against worldwide social inertia by FPA's and by individuals in them. In the United States, for example, one can cite:

Planned Parenthood's Honorary Chairmanship to Dwight D. Eisenhower in November 1964, which gave him the opportunity to reverse publicly the stand he took against US government involvement in birth control in 1959 (3).

Dr. Alan Guttmacher's testimony to the US Senate in August 1965 in favor of Senator Gruening's initiative that led to strong Congressional support of family planning within two years (4).

Planned Parenthood's 50th Anniversary dinner in May 1966, which provided guest speaker Wilbur J. Cohen, then Under Secretary of Health, Education, and Welfare, the opportunity to create and announce establishment of a new post of Deputy Assistant Secretary for Population (5).

Dr. Guttmacher's testimony to the US Senate in December, 1969, supporting the Tydings bill which became the Family Planning and Population Research Act of 1970 (6).

Multiple effective inputs by staff of Planned Parenthood's Alan Guttmacher Institute in development of the nation's first Five Year Plan for Family Planning Services and Population Research Programs (7).

What effects have government family planning programs had upon private family planning associations? The latter might be expected to fade slowly away as their major missions were accomplished. What would be left to do once governments had not only changed laws and regulations from blocking to supporting family planning, but also directly assumed the service and information functions that the private associations formerly carried alone? Organizations have enormous inherent tenacity to survive, but what would they do and who would pay for them once the government was doing everything?

The time scale is short, but the actual effect of government involvement in family planning has been the opposite. With few exceptions, family planning associations have grown and flourished as governments suddenly stopped being barriers and became sources of legal, social, and economic support. The growth of IPPF in members, funds, and staff is shown in Table II. In the 1962–72 decade, as government programs came into being throughout the world (Table I), IPPF's member associations increased 2½ times; its staff increased 15-fold; its expenditures from private sources increased 10-fold; and its expenditures from government sources increased 88-fold! Governments found they needed the experience, expertise, commitment, and ability that often only IPPF and its affiliates had and would make available, to operate and innovate outside government in this new, still controversial field.

The effects upon national family planning associations have been examined and partially documented by IPPF (8 9) and the United Nations (10). While growth of most national associations has been in expanded provision of contraceptive services and supplies, most attention in these studies has been to new or expanded activities which complement the service and supply functions it is assumed governments eventually will provide directly. Among activities being performed by private associations and encouraged to meet future needs are: training of personnel; community education and information; distribution of

TABLE II

Growth of IPPF, 1952–72

	1952	1957	1962	1967	1972
Number of Member Countries					
Full:	8	16	19	30	50
Associate:	—	4	10	19	27
Affiliate:	–	2	2	2	2
Total	8	22	31	51	79
Annual Expenditures by Sources (Thousands of $)					
Private:	?	23	30	3,300	3,025
Government:	—	–	—	736	23,375
Total:	?	23	30	4,036	26,400
Staff					
Professional:	2	5	8	28	85
Support:	1	3	5	30	110
Total:	3	8	13	58	195

Source: From Corsa, L. and Oakley, D.: *Population Planning* (in preparation).

nonclinical contraceptives; youth programs; policy development and legal reform; research and evaluation; and innovation and trial of new ideas.

Actual experience of individual FPA's as their governments became involved in family planning has yielded a wide range of alternatives from the exceptional extremes of elimination of the private association to sole reliance upon the private association funded primarily by the government.

The latter arise in special situations where private associations were well established before government involvement. Their continued visibility is felt to avoid open religious and political conflict. For example, family planning services were begun in Hong Kong in 1936 by the private Hong Kong Eugenics League, and revived after World War II by the new Family Planning Association of Hong Kong in 1950. Services were initiated in government health clinic facilities, welfare centers, and facilities for wives of Armed Services personnel. The Association was a Founder Member of IPPF in 1952. The Hong Kong government began partial financial support in 1955 and has increased it significantly each year, as has IPPF since 1964. The Association is the prime source of family planning service in Hong Kong, although in October 1973, the government took over direct operation of family planning in MCH Centers (11).

The classic example of complete substitution by government for private association services is Singapore. Family planning services were started in 1949 by the new Singapore Family Planning Association. Over the years, the Association utilized government facilities and received increasing government financial support. One of IPPF's Regional Offices was located in Singapore, and IPPF's 7th International Conference was held there. Following establishment of the official Singapore Family Planning and Population Board in 1966, almost all family planning service functions, staff, and funds were transferred from the private association to the government board by 1968. In late 1971, the Association reestablished itself to serve in a subsidiary and complementary role to that of the Board (12).

The usual effect of introducing government family planning programs has been for the family planning association to expand its services with financial support from the government and from IPPF, and to take on additional special functions such as training and public education, thus becoming partners in government program development (9). What kind of partner and how active has depended upon: 1) the preexisting size, quality, and political support of the FPA; 2) the interest, energy, and creativity of FPA leaders and staff in expanding clinical services and in developing new activities; 3) the interest and ability of health services to assume FPA clinical functions and expand services at the same time; and 4) the judgment of government program leaders as to how willing and able or troublesome and threatening the FPA would be if participating under government policies and procedures.

The cases of Malaysia and the United States are similar and reasonably typical. Private association services were well established in many major cities, serving largely middle- and lower-middleclass families, approximately five percent of those potentially needing public services. Many of these FPA services were already within government health centers and hospitals. Association leaders and staffs, to whom family planning services were not new or frightening, were more ready to expand services than were most health and hospital leaders and staffs. Government program leaders felt that more rapid program expansion was in their interest and that the private associations offered considerable program support. Government funds were used to finance private association services that complied with new government regulations. But association leaders in turn often influenced the regulations so that they were more flexible, assuring greater ease of access to the services and adequate choice of methods. In this situation, private associations also had greater incentive to be effective proponents with legislators and finance officials for adequate financing of programs.

What does the future hold for private family planning associations as governments become increasingly involved not only in family planning services but also in all other aspects of population planning? IPPF's Ninth International Conference in England in 1973 addressed itself to this question and began to formulate answers to guide the international agency and its affiliates at this time (13). National organizations and their local affiliates in each country are at different stages of dealing with the question.

The perpetual answer is that to the extent that salient social problems are multiplied by changes in population, they require the attention of people who understand the determinants, consequences, and control of population change. In whatever way the world and its nations are divided and organized, multiple means are needed to bring such individuals and groups together to think through, plan ahead, and try out on a limited scale the most rational ways to resolve population problems. Private FPA's are one important means in most countries where they usually will be supported by their societies and governments for that purpose. Governments themselves have limited capacities to look or plan very far ahead, and even more limited abilities to act early to prevent serious problems that are foreseen but are not immediate. A government may see a particular private organization as sufficiently troublesome or threatening that it will try to destroy it by cutting funds. Strong citizen support and a strong international organization are particularly essential at such times.

For the shorter run, more specific answers are possible in terms of activities like those listed earlier. The usual assumption that contraceptive services and supplies will be adequately provided by the normal mix of public, private nonprofit, and commercial health care services needs challenge on the basis of experience so far in advanced countries like Sweden, Japan, England, Netherlands, and the United States. At the least, some group like FPA is needed to monitor whatever systems are used to be sure they are serving people well, and to be advocates with power to effect corrective change when the systems are malfunctioning. The historical inability of health care systems primarily concerned with treating the sick to pay sufficient attention to preventive care will apply even more to the prevention of unwanted pregnancies which requires sustained vigilance and prompt response. We may find that some contraceptive service and supply functions are best provided in communities through a specialized agency whose staff and outlets are specially concerned about and geared to such personal needs of so many people. In any event, FPA's will require multiple means of real interaction with the community and nation on which are based their larger purposes: education, evaluation, research, innovation, and policy leadership. How well family planning associations provide leadership and innovation and interact effectively with people and governments in meeting population problems of the future will depend on their ability to attract and support persons of vision, compassion, and commitment like Alan Guttmacher to follow in his steps.

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Maternal and Child Health and Family Planning Services: The Contemporary Global Picture

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Alan F. Guttmacher's active professional career as obstetrician, reproductive scientist, teacher, and humanist spanned half a century. During this entire period he practiced and preached, with unwavering devotion and dedication, improvement of the quality of life for all—but specifically for mothers, children, and family. There is a sense of divine coincidence and perhaps of prophetic fulfillment that he died in 1974– World Population Year. This was the year of the World Population Conference in Bucharest which enunciated the World Population Plan of Action designed "to improve the quality of life of the peoples of the world," the very same ideal to which Doctor Guttmacher directed his boundless energy.

Introduction

Exponential population growth and overpopulation have generated unprecedented dialogue within the world community of nations. This is a salutary phenomenon. The concerns engendered by the population problem have developed a priority of interests among political, social, economic and health professionals and planners, worldwide, toward improvement of the quality of life. A World Population Plan of Action designed "to improve the quality of life of the peoples of the world" was adopted by consensus of the 137 governments participating in the World Population Conference in Bucharest. Reflecting political as well as demographic pressures, the Plan of Action calls for socioeconomic development as well as health and family planning programs designed to reduce excess fertility (1).

Maternal and Child Health and Family Planning (MCH/FP) considerations assume high priority in the implementation of such planning and encompass a broad spectrum of services and activities responsive to the major health problems of mothers, children, and families. Program objectives are both short- and long-range. Immediate objectives are to improve the health of mothers and children. Long-range objectives are concerned with the improvement, protection, and promotion of human development to assure improved lifelong individual, family, and community health. To attain these objectives, the interrelation of maternal, child, family, and community health must be an all-pervading concept. In global perspective, however, this concept of MCH/FP is relatively new on the world health scene.

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To appreciate the novelty of this concept, a brief historical review is in order. A mere quarter century has elapsed since the First World Health Assembly, meeting in Geneva on 24 June 1948, adopted resolutions to establish The Expert Committee on Maternal and Child Health to act as an advisory body to WHO and to set up a Section on Maternal and Child Health within its Secretariat.

From this initial mandate, MCH/FP programs have developed by stages during the past 25 years. Stage one was concerned with starting demonstration and training projects and then moving to a more comprehensive coverage of the population by establishing networks of maternal and child health centers.

In the second stage, efforts were directed towards integration of MCH services into the general health delivery system.

The third stage concentrated on education of pediatricians, pediatric nurses, and public health nurses, and the training of auxiliary nurse-midwives (2). Most importantly, it was during this stage that the Twenty-First World Health Assembly recognized "that family planning is viewed by many Member States as an important component of basic health services, particularly of maternal and child health, and in the promotion of family health, and plays a role in social and economic development (and) that every family should have the opportunity of obtaining information and advice on problems connected with family planning, including infertility and sterility" (3).

The fourth stage placed emphasis on the quality of life of the individual and family. Family planning was recognized as a preventive health measure. Family planning activities were not only developed, but also integrated into the maternal and child health or general health services. In addition, coordination of nutrition and family planning activities, and the expansion of teaching and research in the fields of human reproduction, family planning, and population dynamics got under way. Since 1970, when the family health program concept was instituted, there has been acceleration of activity in the behavioral aspects relating to the family and its environment. Since these additional activities require additional professional and paraprofessional manpower, training and manpower development has been expanded. Priority is being given at this current stage to training of teachers, supervisors, and administrative leaders, and, wherever possible, to the introduction of integrated teaching programs on the health aspects of family planning, population dynamics, and human reproduction into the basic curricula for health personnel at all levels (4).

Major Health Problems of Mothers and Children

A survey for the World Health Organization of maternal and child health and family planning activities and services throughout the world was recently completed by the author (5). The purpose of the survey was to elucidate the current major health problems and to put into perspective the need to expand MCH/FP activities and to integrate them more specifically into general health services.

From this global overview, a number of basic important and correctable problems became evident, namely:

High maternal, infant, and childhood mortality;
Shortages and or maldistribution of health manpower and facilities;
Disparity in government allocation of budgetary funds for health;
Inequality in provision of MCH/FP services; and
Lack of adequate registration and reporting systems.

Of equal importance, the overview pointed up the tragic gap in availability, accessibility, quantity, and quality of MCH FP services between the developed and the developing nations of the world and between the urban and rural populations of all nations.

There is consensus in viewing global health needs that mothers and children comprise two of the groups most vulnerable to disease in any population. Actually, two-thirds of all health care services are devoted to the health problems of mothers and children. Their major health problems, whether in developing or developed countries, are probably determined more by cultural, social, and economic factors than by geography. Thus, there are not only differences between global regions and the countries they include, but also between different parts of the same country. This accounts for the variations in scope and administration of maternal and child health services from country to country.

Despite these differences, there emerges a commonality of health problem profiles—a triad of infection, nutrition, and reproductive problems, which in turn establishes the commonality of MCH FP objectives: reduction of maternal, perinatal, infant, and childhood mortality and morbidity; and improved physical, mental, and social health for the individual and the family.

Maternal, Infant and Childhood Mortality

Despite overall improvement in the basic indices of maternal and child health, wide disparities (in these indices) still exist between the developing and the developed nations, the highest mortality levels in the developing countries.

a. Maternal Mortality. Despite a consistent downward trend during the past quarter of a century, high rates persist except for the developed nations of Europe, North America, and Australia. Maternal mortality rates are 5 to 10 times higher in Middle and South America (15.0 to 26.0 per 10,000 live births) than in North America (2.5 per 10,000 live births). In other countries, reported rates are as high as 92 in Uganda (East Africa), 60 to 80 in India (Southeast Asia), 20 to 22 in Philippines and Western Samoa (Western Pacific), and 13 in Turkey (Europe).

Factors producing these marked differences in pregnancy outcome for mothers display a common pattern. Basically, the social, economic, and environmental factors in the developing countries are extreme poverty, illiteracy, food shortages, housing, and environmental sanitation deficiencies.

Superimposed on this base is the pattern of early marriage, repeated pregnancy and lactation, plus anemia, abetted by protein-calorie malnutrition, intestinal parasitism, and often malaria, as the basis for "maternal depletion." The maternal depletion syndrome sets the stage for the major causes of maternal mortality and morbidity, namely, hemorrhage, infection, toxemia, and obstructed labor.

Additionally, high fertility, pregnancy at early and late extremes of the reproductive age span, high parity, and the inability to space pregnancies create the problem of induced, extra-hospital abortion as an additional major cause of maternal mortality and morbidity.

Finally, the high incidence of late or no prenatal care and up to 90 percent domiciliary delivery, either totally unsupervised by a birth attendant or at best supervised by poorly or inadequately trained birth attendants, complete the vicious cycle. These latter facts highlight the inadequacy, both in numbers and distribution, of trained health professional manpower and of adequate health care facilities.

b. Infant Mortality. Mortality in the first year of life is not only a good basic index of MCH care, but also a relatively sensitive index of social and economic development. Despite moderate downward trends over the past 25 years, infant mortality in the developing world is from 3 to 17 times higher than in the industrialized regions of Europe and North America. Interregional variations reveal marked differences also. Reported infant mortality rates in Africa range from 52 in Mauritius to 216 in Guinea; in the Americas from 18.0 and 17.5 in USA and Canada to 92 in Chile and Ecuador; in the middle East from 23 in Israel to an estimated 400 in Afghanistan; in Europe from 11 in Sweden to 119 in Turkey; in Asia from 12.5 in Japan to an estimated 139 in India.

The relationship of the early neonatal component to total infant mortality differs significantly between developed and developing nations. Table I compares 10 selected developed with 10 selected developing nations. In the developed nations, two-thirds of the infant mortality occurs in the early neonatal period. In the developing nations, 66 percent to 94 percent of infant mortality occurs after the early neonatal period. This observation reinforces the vulnerability of infants in the developing countries during the postneonatal period to the lethal syner-

TABLE I

Relationship of Neonatal Mortality (1968) to Infant Mortality (1972)
Rate per 1,000 Live Births

Selected Developed Countries	Early Neonatal	Infant Mortality	Selected Developing Countries	Early Neonatal	Infant Mortality
Canada	12	19	Ghana	23	122
USA	14	19	Kenya	29	119
United Kingdom	12	18	Chile	22	92
Sweden	8	11	Ecuador	13	91
Denmark	10	15	Albania	6	87
Finland	10	12	Egypt	8	119
Netherlands	8	13	Kuwait	12	39
Norway	9	14	India	19	139
Australia	12	18	Thailand	13	26
Japan	7	13	Philippines	23	67

gism between protein-calorie malnutrition and infection, particularly respiratory and gastrointestinal infection in the malnourished infant.

Noteworthy, also, is the approximately 2 times higher early neonatal and up to 6 times higher infant mortality in the developing countires.

Tetanus is a cause of more than half the neonatal mortality in developing countries in some areas (6). Other major causes of neonatal mortality include low birth weight and immaturity, birth injury, and congenital malformations. The average birth weight of infants is lower in many developing countries than it is in developed countries. There is good reason to believe that the difference is not of genetic origin, but is due largely to maternal malnutrition (7).

c. Childhood Mortality. Mortality in children under 5 years of age is in the range of 50 percent of the total mortality in the developing nations, in tragically sharp contrast to a median of less than 5 percent of the total mortality in the developed countries. The exogenous risks of malnutrition and nutritional disorders, infection, parasitic infestation causing severe anemia, and accidents are the major causes of mortality in this age group.

Provision of Health Services

Health care delivery is a basic social, economic, and public health problem. It involves the need to reach the entire population and to equalize not only the availability and accessibility of health care but also the quantity and quality of the health services rendered.

Unequal provision of MCH/FP services is common to all countries, whether developed or developing. Even in the most highly industrialized nations there are large segments of the population that are ill-served by the health care delivery system, for example, the inner city ghettos of the large metropolitan areas and the remote rural areas in the USA. Faced with shortages and maldistribution of health manpower, facilities, and finances, solutions to this problem are even more complex and difficult, though not unsurmountable, in the less developed countries.

A practical long-term international strategy for integrating curative, preventive, and promotional health services into a comprehensive health care system is developing. Basic health services are being strengthened and expanded into the rural and peripheral areas; these peripheral health services are being staffed by health auxiliary personnel who are actively recruited, well trained, and adequately supervised by the better trained health professionals. Thus, provision of improving quality of health care to the total population is increasing.

These steps obviously infer the strengthening and further integration of MCH/FP services into the general health infrastructure. A major impetus to implementing this concept has been the development of maternity-centered family planning activities. The purpose of this approach is to use the maternity cycle to educate and motivate women to the health benefits of family planning and, conversely, to use family planning activities to promote and augment acceptance and practice of MCH services.

Perhaps the first major effort in this direction was taken by the Population

Council in 1966 by initiating an International Postpartum Program designed to introduce family planning information and services to women securing maternity care in large urban maternity hospitals around the world (8). Almost simultaneously, extension of this concept to peripheral rural areas was proposed by developing networks of rural MCH centers and substations through which integrated services would include antepartum care, supervised delivery either in MCH center, substation, or home, and postpartum follow-up care to mother and infant as well as education, motivation and provision of family planning, nutrition and general health services (9–11).

The core components for such integrated MCH/FP programs are maternal care, family planning, and nutrition and health education services. When these are firmly established, other important MCH services such as day care, child care, school health, care of the handicapped child, genetic counseling, and youth and adolescent care should be added. Such integrated services, when, and if achieved by all countries may permit achievement of the ultimate goal of truly comprehensive family health care for all.

a. Maternal Care. Quantitative assessment of the extent and quality of maternal care is difficult at the present time because of reporting deficiencies, inconsistencies, "guesstimates" or responses of "no information available" from the majority of developing nations. However, it can be generally accepted that in the developing countries 10 to 20 percent of pregnant women receive prenatal care; in the developed countries approximately 75 percent of pregnant women have had prenatal care prior to delivery.

Global review of delivery services for the years 1969–1971 reveals that approximately 50 percent of births are conducted in hospital, ranging from a low of 3 percent to a high of over 99 percent. It is obvious that the percentage of in-hospital delivery is high in the developed countries and low in the developing countries. Conversely, domiciliary deliveries are exceedingly high in the developing nations.

The percent of births conducted by trained health professionals (physicians, nurses, midwives, and trained auxiliaries), whether in hospital or at home, varies likewise from as low as 12 percent to as high as 100 percent. There are many countries where up to 88 percent of the births are conducted by nonprofessional, untrained persons (traditional birth attendants, indigenous midwives, neighbors, or family members). The general observation is valid that the highest incidence of untrained attendants at delivery is found in the less developed nations. How this correlates with the high maternal, perinatal, and infant mortality in the developing world can only be inferred. Until trained professional health manpower becomes sufficiently available to attend or supervise all deliveries, whether in hospital or at home, the traditional birth attendant will continue to play a role in delivery services. Thus, their registration and supervision of their activities as well as their training and support must be a high priority maternal and child health responsibility.

b. Family Planning. The interrelationships between population problems and the health aspects of human reproduction, family planning, and population dynamics have emerged as a priority consideration in the thinking of social, economic, and health planners worldwide only during the past decade.

Family planning refers to practices that help individuals or couples avoid unwanted births, regulate the intervals between wanted pregnancies, control the time at which births occur in relation to the age of the parents, and attain desired family size.

Since 1965, the growing conviction that family planning is a preventive activity within health services has led many of the 138 nations in the United Nations "family" to review, revise, or develop their laws and policies. Thirty countries have adopted official family planning policies either to reduce the population growth rate or for health reasons or as a human right. There are 63 countries which give "official support" to family planning for reasons of health and/or as a human right—in other words they support family planning activities for other than demographic reasons. There are 36 countries that neither have a "policy" nor "support" family planning for any reason. It is not possible to ascertain the position of 9 countries at this time. The vast majority of the 36 countries with neither "policy" nor "support" for family planning are in Africa (18 countries) and the Eastern Mediterranean (13 countries). However, under the stimulus of World Population Year and the recent World Population Conference in Bucharest, the tempo of discussion has accelerated markedly, so that the negative position of these countries may change in the near future.

In 84 of the 93 nations that have official policy or official support of family planning, these activities are integrated into maternal and child health or general health services and in many of them family planning activities may also be provided through voluntary family planning agencies and by the private medical sector, which does occur in the 9 countries that have not integrated family planning into the health services.

c. Nutrition. The commonality of MCH objectives, to reduce maternal, infant, and childhood mortality and morbidity and to improve the quality of life by improved physical, mental, and social health for the individual and the family is intimately related to nutrition.

The relationship of nutritional deficiencies to maternal depletion, fetal loss, low birthweight, and maternal mortality and morbidity is well documented, as is the synergism of nutritional deficiency and infection to infant and child mortality. There is also growing consensus that malnutrition, particularly in the latter weeks of pregnancy and during the first year of life, not only affects physical growth and development, but also may seriously jeopardize mental growth and development.

As previously pointed out, protein-calorie malnutrition in combination with infection is a major concern for the developing nations, since up to 50 percent of childhood mortality may be due to this lethal combination.

In response to these facts and concerns, more and more nations, particularly in the developing world, are beginning to incorporate food and nutrition policy into the planning for their socioeconomic development. In addition, they are seeking technical assistance and financial aid to enable them to expand nutrition activities in their health services, to organize supplementary feeding programs, to establish nutritional rehabilitation centers, and to provide nutrition education and training not only to all categories of maternal and child health workers but also to consumers (mothers, children, and families).

d. Health Education. National health authorities are now aware that health education is an essential ingredient in integrated MCH/FP activities for health promotion and protection, the success of which depends upon active participation by a well-informed community. Thus, the health educator is an increasingly important member of the multidisciplinary health professional team. As with all health personnel, there is a global shortage of health educators. Fortunately, recruitment and training of such personnel are expanding yearly.

In addition to a role in all aspects of MCH/FP activities, the health educator has important responsibilities in health-related services for environmental sanitation, nutrition, and communicable disease control as well.

It is timely to expand health education horizons in order to reach community leaders who are or may be responsible for shaping health policy. This means attempting to educate political leaders, governmental authorities, cultural, civic and welfare leaders, and finally, respected and influential tribal and local leaders, particularly in the developing countries' more rural areas, so that they can mold opinions of the populace.

Thoughts for the Future

The current status of the problems and needs related to MCH/FP, reveals a complexity of etiologic factors. Future progress must depend on coordination of problem-solving strategies.

As a first and basic step, governments of the high risk, developing countries must face the inescapable need to correct social, economic, and environmental pathology.

The allocation of higher percentages of health budgets to MCH/FP services as part of general health structure is imperative.

Continued expansion of MCH/FP services to the most remote rural areas so as to reach all the vulnerable population of mothers, children, and families, must be unremitting. Inexpensive family-centered health clinics with attached small maternity and child care facilities should be developed as peripheral networks, thus expanding delivery of MCH/FP care to the areas where the need is greatest.

Recruitment and training of indigenous community persons to function as auxiliary health personnel, under supervision and guidance by better trained health professionals, can take up the slack of shortages of physicians, nurses, and trained midwives. This would augment the health protection and health promotional MCH/FP activities of early immunization, ongoing surveillance of physical, neurologic and emotional growth and development, nutritional guidance and food supplementation, improvement in environmental sanitation, and continuing education of parents in sound principles of parentcraft and home management. Additionally, this would facilitate expanded availability and accessibility of family planning services.

Concomitantly, health education and health promotion campaigns must be undertaken, to orient the most vulnerable population groups to understand and to use the health promotional, preventive, and curative services that are available; and to accept the trained health auxiliary as the primary provider of these services. Such measures can expand and augment the family- and maternity-centered health care programs. This would ensure delivery of at least a minimum of preconceptional, antepartum, delivery, postpartum, family planning, and infertility care to women, and well baby, sick child, and health promotional services to children and youth, as well.

In addition, continuing support should be provided to expand teaching of human reproduction, population dynamics, and family planning in the medical, nursing, midwifery, and paraprofessional training schools throughout the world, so that the health professionals of tomorrow will be versed in these important aspects of MCH/FP care.

The integration of such concepts into existing health structures will reach those in the population previously unreached with these services. The development of such MCH/FP services by the developing countries will pay off in greater dividends than investing in sophisticated maternal and newborn facilities and equipment in emulation of the more developed nations.

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Knowledge, Perception, and Change: Notes on a Fragment of Social History

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In a rapidly changing world, knowledge of how change is brought about remains primitive. Many controversies, to be sure, reflect disagreements over the desirability of the proposed changes themselves, but even individuals who share common objectives often find themselves in conflict, not over the ends to be sought, but over the most appropriate means. The dispute over these instrumental issues is attributable in some measure to the fact that the ways in which change is brought about often have not been specified and analyzed, either by the actors themselves or by noninvolved observers.

Public policy on fertility control changed radically in the United States in the past two decades, and these changes resulted in significant modifications in the behavior of institutions and individuals (1). The US Planned Parenthood movement had as one of its major goals stimulation of these policy changes, and many analysts credit the movement with playing a critical, even decisive, role in accelerating them. Planned Parenthood's ability to influence the course of events, in turn, depended on important changes in its own underlying assumptions about what was necessary and possible.

How these various changes came about and the interactions among them would make an excellent case study of the process of social change which might have more general applicability. As a contribution toward such a study, I shall describe some of the factors which led to modifications of the basic assumptions held by the Planned Parenthood movement in the 1950's, modifications which I believe were essential preconditions for the movement's success in the 1960's. Since I participated in many of the events under discussion, this presentation gives only one view of a complex process and inevitably must be influenced by hindsight; other participants might place greater emphasis on other factors.

One further caveat seems necessary. Like other organizations and movements, Planned Parenthood is a complex organization, composed of diverse individuals with related but differing perceptions, interests, and goals. Many of its important transactions are conducted indirectly rather than through formal processes of deliberation and resolution. Under such circumstances, it is difficult to identify an "overall" Planned Parenthood viewpoint or outlook. Yet such an outlook is a sine qua non in any organization and can be abstracted from its expressed or implied statements and actions. When I describe a viewpoint held by the movement, I will be referring to the abstracted collective understanding we more or less shared (sometimes without being aware of it) of the shape of the world we lived in, our historic mission, and most importantly, of what we believed was in the realm of the possible.

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The US Planned Parenthood movement historically has been committed to two central theses: 1) that rational and efficient control over fertility is an instrumental intervention necessary for individual and societal welfare; and 2) that a voluntary organization such as Planned Parenthood, acting as an agent of change, is necessary to accelerate achievement of rational fertility control. Two decades ago, Planned Parenthood's volunteer leaders and professional staff reflected the diverse range of interests which have characterized the movement. Its goals, expressed in the slogan, "Babies by Choice, Not by Chance," were broad enough to encompass concern over women's rights, marital happiness, and sexual fulfillment, as well as the adverse medical, emotional, and economic consequences of frequent and excessive childbearing. The relationship between unregulated fertility and poverty had long been an important part of the movement's philosophy and continued to provide a principal focus for its activities. During the 1950's, however, this was beginning to be paralleled by concern over the relationship between unregulated fertility and population growth—a concern which led ultimately to adding demographic objectives to Planned Parenthood's traditional purposes. In US society at that time, birth control was viewed, paradoxically, both as an intensely controversial subject and as a problem which was largely "solved" among the middle and upper classes, the bulk of the US population.

From its own experience and in the light of such contradictory evidence as the widespread practice of illegal abortion, the Planned Parenthood movement could not regard the problem as "solved" in any real sense for large segments of the US population. It saw its main roles as educating public and professional opinion to the significant tasks remaining; striving for the full legitimacy of birth control in law, policy, and public opinion; and completing what Himes had described as "the democratization of birth control"—the extension to low-income persons of scientific methods of fertility regulation (2). The delivery of contraceptive services by affiliated clinics was regarded as a demonstration program contributing to the movement's ability to carry out each of these roles. The first role was exemplified in such activities as sponsorship of a major conference on legal and illegal abortion, held at Arden House in 1955*, and a continuing program to enlist distinguished medical leaders and gain professional acceptance (such as the 1959 policy statement of the American Public Health Association). The second encompassed local efforts to invalidate restrictive laws and gain acceptance in community councils, as well as an intensive national campaign to break the barriers to discussion of birth control in the mass media. The third took the form of a program to encourage affiliated clinics actively to reach out to groups needing services. At the same time, however, it became increasingly evident that the task of "democratization" could not be accomplished by a private organization alone but required the participation of the established health system, particularly the part operated by government that sered lvow-income persons. This realization brought the movement into direct confrontation with the prevalent view that the issue was too controversial for public officials and institutions.

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* Cf. *Abortion in the United States*, Edited by M. S. Calderone, Hoeber-Harper, New York 1958.

If the movement's long-range goals and intermediate objectives were reasonably clear, the means to advance them were less certain. Each of the goals and objectives required social change and innovation, which implied that it would be resisted by existing institutions. Planned Parenthood shared the dilemma faced by many organizations in similar circumstances—to contend, or to cooperate? Its ranks included advocates of conflict as well as of cooperation, and its actions often reflected both viewpoints. Yet more fundamental ideas of what was realistically possible shaped even the judgments of advocates of these contending strategies. In the mid-1950's, the Planned Parenthood movement viewed its potential as constrained by technologic, political, and sociologic factors essentially beyond its control:

Technologic

The movement, dominated professionally by obstetricians and gynecologists, was almost entirely dependent upon the diaphragm-and-jelly technique, which was regarded as the most effective existing method of contraception. But its own clinical experience attested to the unsuitability of this method, as well as other conventional techniques, for many couples. Without a better technology, many Planned Parenthood leaders did not expect to make much progress.

Political

The prevailing view held that Catholic opposition to birth control was *the* political problem—that is, the only one worth being concerned about. The Catholic Church was seen as having sufficient power and influence to prevent both governmental and private institutions from adopting more favorable policies.

Sociologic

While the technologic and political assumptions were explicit, the sociologic assumptions were more implicit. The perceptions of some in Planned Parenthood were shaped by two underlying fears about the likely course of events even if the technologic and political constraints could be overcome. The first was that the poor "wouldn't use contraception if they had it," as Margaret Sanger had been told by physicians and upperclass professionals four decades earlier (3). The second was an uneasy feeling that physicians and medical institutions would not be interested in serving as distribution channels for birth control because its importance was regarded as primarily social, not medical.

These assumptions established the parameters of an equation which, in the dominant view, set sharp limits on what could be expected. They were formed over many years and reflected assessments which may have been partially or wholly valid at the time. But like many such "givens," they were rarely subject to reappraisal in the light of changing conditions. In the 1950's, the US was changing in many significant ways. These changes, reflected in events as well as in social trends monitored by research findings, helped to dislodge the movement's fundamental assumptions and replace them with others more conducive to taking advantage of the opportunities which emerged in the 1960's.

The perceived technologic constraint gave rise to Planned Parenthood's interest in stimulating research for improved contraceptive methods. The movement's response ranged from generating the first "seed money" to support Gregory Pincus's work on what was to become the hormonal "oral" contraceptive to the initiation of a small grants-in-aid program administered by the Federation's Biological Research Committee and encouragement of clinical research on new methods in affiliated clinics. A high point was reached when Planned Parenthood and the Population Council jointly sponsored an important international conference on biomedical research related to conception held at West Point in 1959.*

There were ambiguities, however, in the concept of "improved" methods. The criteria included greater efficiency in preventing conception and application at a time unrelated to sexual intercourse. By other criteria, however, "improved" methods would be those which could be dispensed through nonmedical and nonclinical channels. When Planned Parenthood held a symposium in 1957 to review the progress of research for new methods and to assess the likely effects of their development †, this divergence was evident. Many were led to expect the advent of "simple" methods which would be more effective because they would be used more regularly, and used more regularly because they would require no medical intervention. This viewpoint was based in part on the underlying sociologic skepticism both about physicians and the poor and its corollary that low-income persons could not be expected to seek guidance from physicians.

Partly as a result of these contradictory concepts, the Federation was in many ways unprepared in 1960 for the marketing of the pill, which constituted a "simpler" (i.e., coitus-independent) method requiring more medical supervision, not less. More than 18 months of careful education and persuasion by the Federation's medical director was required before the pill was accepted by PPFA's Medical Committee and most Affiliates offered it to patients. Despite the fact that new methods were viewed as essential, particularly for low-income persons, little attention was given to the changes in Affiliate programs which would be needed following the introduction of the pill. In its first forms, the pill was costly, and most Affiliates could not afford to subsidize its distribution. Nevertheless, Affiliate caseloads (composed primarily of low-income women) actually tripled between 1960 and 1965 and it was hard for the organization to keep up with very rapid growth. Yet this very experience, unsettling as it was to many, was seen by others as challenging elitist biases about the poor and confirming one of the movement's major premises: technologic change had led to significant behavioral change. Moreover, the rapidity of the change suggested an additional premise which was a precondition for a serious effort to change public policy: the oral contraceptive (soon joined by new intrauterine devices) provided a technology which for the first time made possible large-scale programming in a realistic way.

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* Cf. *Mechanisms Concerned with Conception*. Edited by C. Hartman. Macmillan, New York 1963; Hartman, C.: Physiological Mechanisms Concerned with Conception An Inventory of Answered Questions, *Perspectives in Biology and Medicine*, Vol. IV, No. 1, 1960; Also, S. Zuckerman, *Science*, 6 November 1959.

† Cf. *Simple Methods of Contraception*. Edited by W. Best and F. S. Jaffe, Planned Parenthood Federation of America, New York 1958.

The perception of the birth control issue as primarily or exclusively a "Catholic problem" was not limited to the Planned Parenthood movement, but dominated thinking on the subject by opinion-molders and decision-makers; this simplistic notion persists to some degree even today, despite all that has happened in the last 20 years. The sharpest confrontations between the movement and the Catholic Church had, of course, occurred in the 1920's and 1930's. By contrast, the mid-1950's were relatively tranquil—and relatively static. While "Catholic power" no longer was used to shut down Planned Parenthood clinics or public meetings on birth control, less visible manifestations of Catholic influence thwarted even discussion of the subject, much less advancement of birth control objectives, in government, the media, the scientific community, the health professions, and social service institutions. Lacking a feasible strategy either for overcoming or neutralizing the Church's opposition, Planned Parenthood, like other movements in similarly polarized situations, was to a large extent reduced to efforts to embarrass the opposition or win debaters' points. However brave the overt verbal expressions, the implicit view was acceptance of the status quo unless and until the Church could be brought to change its doctrine.

A turning point for Planned Parenthood began in 1955 when Agnes Meyer, the noted civic leader, admonished the organization:

> The Catholic Church has the right to defend and promulgate its ideas on birth control as much as any other group. If non-Catholics were as honest and forthright in advancing their theories, the influence of the Catholic Church would be confined to its own members and the fog of obscurity, vacillation and cowardice which surrounds the need for a nationwide contraceptive program would be dissolved.*

This was a breathtakingly simple notion that somehow had eluded many in Planned Parenthood: if non-Catholics could be persuaded to preach what they practiced, sufficient support could be generated to move forward. Instead of wasting time in futile doctrinal arguments with the Catholics, the emphasis should be on building a visible coalition expressing the breadth of non-Catholic support. Non-Catholic reticence about supporting birth control was linked to fears of Catholic retaliation, and Planned Parenthood had to learn how to deal with these fears, real or imagined. But Mrs. Meyer's strategy implied a substantial shift in Planned Parenthood's focus.

The most extensive expressions of this strategy were the events, culminating in 1958, which led to the reversal of the ban on contraceptive prescription in New York's municipal hospitals. These events have been described elsewhere† and it is sufficient for our purposes to note that the campaign had at least two far-reaching results. First, it made public and visible support for birth control from virtually all non-Catholic religious, professional, and secular groups (as well as from some Catholics) —a coalition far broader than previously had expressed itself on this issue. Second, the settlement of the controversy detailed the terms of a public policy appropriate to a pluralistic society, under which Catholic patients and professionals would be free to follow their Church's teachings but would be precluded from preventing non-Catholics from following their own consciences. This has become the basic predicate of virtually all subsequent changes in public policy on fertility control, whether expressed in legislation, court decisions, or administrative regulations.

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* Quoted in *Anatomy of a Victory*. Planned Parenthood Federation of America, New York 1959 (mimeograph), p. 23.

† Cf. *Anatomy of a Victory*. PPFA, New York 1959; Guttmacher, A. F.: *Babies by Choice or by Chance*. Doubleday, New York 1959, Chapter 8; Rock, J.: *The Time Has Come*. Knopf, New York 1963; and Hellman, L. M.: One Galileo Is Enough, Eugenics Rev 57:161, 1965.

The New York municipal hospital victory forced a questioning of existing strategic assumptions in Planned Parenthood. If the Church could be successfully isolated in New York—where political observers regularly referred to the Cardinal's residence as "the powerhouse"—why not elsewhere? If a number of Catholics during the campaign dissented from the Church's position on grounds that the Church could not impose its doctrines on others in a pluralistic society, how many others were there who held similar views, and how could they be encouraged to express themselves? What became of the image of the Church as monolithic on the birth control issue? And if the Church was indeed not monolithic, then what became of the perceptions of political leaders that for them to take a stand in favor of birth control was to invite swift retaliation from an all-powerful, monolithic institution?

Within a year of the resolution of the controversy, publication of the results of the 1955 Growth of American Families (GAF) study gave support for this emerging redefinition (4). The study showed that nearly half the Catholic wives approved of fertility control, two-thirds had used or expected to use contraception, and thirty percent had at one time or another used contraceptive methods denounced as immoral by the Church.

If these developments were not sufficient to shatter the monolithic image, additional evidence was soon forthcoming, stimulated in part by the emergence of the pill as a new method of conception control and in part by growing concern over rapid population growth, particularly in underdeveloped countries. In the 1960 campaign which elected America's first Catholic President, important segments of the US Catholic community made it clear they did not support the Church's intransigent official stand. By the mid-1960's, numerous books and articles* had culminated in the historic deliberations of Vatican II and made evident that dissent on birth control within the Church was worldwide. Although a valiant effort was made, in *Humanae Vitae* in 1968, to reassert the traditional doctrine, it was no longer possible for serious observers to regard the Church as united in its determination to block change.†

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* Cf. Rock, J.: *The Time Has Come*. Knopf, New York 1963; Dupre, L.: *Contraception and Catholics*. Helicon, Baltimore, Md., 1963; de Lestapis, S.: *Family Planning and Modern Problems*. Herder and Herder, New York 1961; Roberts, T. D.: *Contraception and Holiness*. Herder and Herder, New York 1964; and Pyle, L.: *The Pill and Birth Regulation*. Helicon, Baltimore, Md., 1964.

† Cf. Westoff, C. V. and Ryder, N. B.: The Papal Encyclical and Catholic Practice and Attitudes: United States, 1969, *Studies in Family Planning*, February 1970; and Stycos, J. M.: *Ideology, Faith and Family Planning in Latin America*. McGraw-Hill, New York 1971, Chapter 16.

By the early 1960s, events had forced many in Planned Parenthood to revise their concept of the nature of the "Catholic problem" and their strategies on how to cope with the political consequences of Catholic opposition to birth control. These events also foreshadowed other serious political obstacles beyond the Catholic problem which would require new assumptions and strategies. But with the collapse of Catholic opposition in the mid-1960's many in Planned Parenthood did not expect that there would be still other, and perhaps more deep-seated, political issues to be resolved. In fact, some expected that the resolution of the Catholic problem would mean that public health agencies could quickly assume full responsibility for provision of contraceptive services, making it possible for Planned Parenthood to "go out of the service business" and restrict its functions to education and research. Such an option was never possible, precisely because of other, largely unrecognized, political issues.

The sociologic assumptions were to prove most difficult to modify, perhaps because they were less explicitly expressed, or perhaps because they "fit" more closely the class biases of many in the organization. The importance of these assumptions is not surprising in an organization which had always seen differential fertility as one of its overriding concerns. In the mid-1950's, the persistence of class and ethnic fertility differentials was puzzling to many in Planned Parenthood: Why didn't more low-income persons come to Planned Parenthood clinics? Weren't they "motivated" to limit their fertility? How could they be educated or persuaded? Questions like these led the Federation to initiate a social research program and to finance exploratory studies by Lee Rainwater of fertility values and practices among low-income persons. To the surprise of some, the studies* showed that low-income couples had considerable desire to limit fertility, as well as experience (largely unsuccessful) in trying different contraceptive methods. But they also demonstrated that low-income couples had a great deal of misinformation about contraception and that their life circumstances made it difficult for them to adapt to the requirements of existing methods, particularly the diaphragm.

Rainwater's findings were read in contradictory ways by Planned Parenthood leaders (and, as he later acknowledged (5), by public health and welfare officials as well). Some viewed them as confirming the persistent elitist bias that low-income persons were really not "motivated" to control their fertility. From this came either passivity ("Why do anything because they wouldn't use it anyway?") or a conceptualization of the required program as one which would somehow instill the required motivation in the target population. The other reading of Rainwater's results was that sufficient motivation already existed but that to assist low-income persons to control their fertility in accordance with their desires would require a very different program—one which was nonjudgmental, made maximal use of the new coitus-independent contraceptive technology, and stressed availability, accessibility, convenience, information, education, and sympathetic continuing reinforcement.

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* Cf. Rainwater, L.: *And the Poor Get Children*, Quadrangle, Chicago 1960; and *Family Design*. Aldine, Chicago 1965.

Before Rainwater's studies were completed, the idea that the principal problem was "motivation" was called into question by a serendipitous byproduct of the clinical testing of new contraceptive products in hospital postpartum clinics. Reports on these tests showed that rates of return for postpartum examinations were much higher than was customary among women who delivered on hospital wards*. If the mere offering of contraceptive consultation and prescription in a postpartum clinic could increase (and even double) the rate of return, how could it be said that low-income persons were not "motivated" to seek and use birth control?

This observation was soon followed by the results of the 1955 and 1960 GAF studies, which were to challenge fundamentally many of these interrelated assumptions. Table I presents selected findings from these studies (together with comparable findings from the 1965 National Fertility Study) and summarizes the overall picture.

By 1960 almost all U.S. couples in all class and ethnic groups expressed a desire for small-to-moderate families, approved of the idea of regulating fertility, and actually had tried to do so with one or another existing contraceptive method. The remaining differentials between socioeconomic groups were minimal. At the same time, however, there was a great deal of unintended fertility, as defined by the couples themselves: many were having more children than they would have preferred or failing to space their pregnancies in accordance with their wishes (Table II).

The incidence of unwanted and mistimed fertility was particularly high among low-income and poorly educated couples, and appeared to be related to their disproportionate reliance on less effective nonmedical methods of contraception (Table III).

These findings had a profound effect on the thinking of many in Planned Parenthood. In a country which typically elects its Presidents by margins of less than five percentage points, 75 to 90 percent approving of anything is the equivalent of virtual unanimity; how then could birth control opponents continue to prevail? The answer was the persisting perception among public officials of birth control as a "controversial" matter; the implication was that Planned Parenthood

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* To my recollection, this phenomenon was noticed and discussed by members of the PPFA Medical Committee in the late 1950's. In 1958, Hilliard Dubrow and Katherine Kuder, reporting on clinical tests at The Mount Sinai Hospital from 1953 to 1957, showed that 84 percent of patients delivering on the Hospital's ward service returned to the postpartum clinic where contraception was offered (Dubrow, H. and Kuder, K.: Combined Postpartum and Family Planning Clinic, Obstet Gynecol 11:586, 1958). At that time, less than 50 percent of ward patients in most hospitals typically returned for the postpartum checkup. The effect of the introduction of contraception on postpartum return rates in municipal hospitals was shown by Hans Lehfeldt. (The First Five Years of Contraceptive Service in a Municipal Hospital, Am J Obstet Gynecol 97:727, 1965). For similar experience in hospitals in other parts of the country, see: Perkin, G.: A Family Planning Unit for Your Hospital? Hosp Pract Vol. 2, No. 5, May 1967.

TABLE I

*Selected Measures of Attitudes Toward Family Size and Fertility Control, and Use of Contraception, 1955, 1960 and 1965**

Subject and Subgroup	1955	1960	1965
Percent Wanting 4 Children or Less			
All Races	· · ·	88	87
White	90	88	88
Catholic	· · ·	· · ·	79
Non-Catholic	· · ·	· · ·	91
Nonwhite	· · ·	85	83[a]
Mean Number of Children Desired			
All Races	· · ·	3.1[c]	3.3
White	3.0[b]	3.1[c]	3.3
Catholic	3.4[b]	3.4[b]	3.1
Protestant	2.9[b]	2.7[b]	3.7
Income >$7,000	2.9[b]	3.3	2.6–2.8[e]
Income <$3,000	3.2[b]	3.3[d]	2.8–2.9[e]
Nonwhite	· · ·	2.7[c]	3.2[a]
Percent in Favor of Fertility Control (Including Rhythm Method)			
All Races	· · ·	93	95
White	74	93	95
Catholic	45	85	93
Protestant	85	96	96
Income >$7,000	87	· · ·	· · ·
Income <$3,000	78	· · ·	· · ·
Nonwhite	· · ·	81	91
Percent Having Used or Expecting To Use Contraception			
White	79	87	90
Catholic	67	80	87
Protestant	83	90	91
Income >$10,000	81	91	92
Income <$3,000	71	82	80
Nonwhite	· · ·	76	86
Percent of Catholics Ever Using Methods Proscribed by Church	30	38	53

Code: a = Negro; b = Number expected; c = Minimum desired; d = Under $5,000; e = Inferred wanted; · · · = Not available.

* Sources: Freedman, R., Whelpton, P. K., and Campbell, A. A.: *Family Planning, Sterility and Population Growth,* McGraw Hill, New York 1959, pp. 156, 166, 181, 221, 276, 293

Whelpton, P. K., Campbell, A. A., and Patterson, J.: *Fertility and Family Planning in the United States,* Princeton, N. J., 1966, pp. 38, 71, 105, 283

Ryder, N. B., and Westoff, C. F.: *Reproduction in the United States, 1965,* Princeton, N. J., 1971, pp. 28, 32, 38, 94, 99, 104, 112, 115, 198

Westoff, C. F., and Ryder, N. B.: Recent Trends in Attitudes Toward Fertility Control and in the Practice of Contraception in the United States, in *Fertility and Family Planning: A World View.* Edited by S. J. Behrman, Michigan 1969, p. 409.

TABLE II

*Proportion of Couples Having Unwanted (Number Failures) or Mistimed (Timing Failures) Births—By Race, Income and Education, 1960**

Race, Income and Education	Number Failures	Timing Failures
White	17	37
Income >$10,000	15	30
Income <$3,000	21	34
Some college	11	36
Grade school only	32	38
Nonwhite	31	43

* Whelpton, P. K., Campbell, A. A., and Patterson, J.: *Fertility and Family Planning in the United States*, Princeton, N. J., 1966, pp. 257, 258, 362.

TABLE III

Use of Less Effective Methods by Fecund Couples Desiring No More Children, By Race and Poverty Status, 1965**

Poverty Status	Percent		
	All Races	White	Negro
Low-Income Couples‡	51	51	54
Other Income Couples**	35	34	43

* Foam, jelly, suppository, rhythm, withdrawal and douche.

‡ Couples with incomes below 125 percent of the Federal poverty level.

** Couples with incomes above 125 percent of the Federal poverty level.

Source: 1965 National Fertility Study special tabulation, reported in Jaffe, F. S.: "Family Planning Services in the United States," Commission on Population Growth and the American Future, Research Reports Volume VI, *Aspects of Population Growth Policy*. Edited by R. Parke, Jr., and C. F. Westoff, Government Printing Office, 1972.

and its allies had not been successful in educating these officials to the simple fact that it was no longer controversial in the practices of the American people. If, in 1955, 78 percent of low-income persons already approved of birth control and 71 percent had used or expected to use it, the implication was similarly clear: What was needed was not a program of exhortation and moral suasion to bring the *idea* of fertility control to persons who had never heard of it; what was needed was a focused effort to identify and overcome the obstacles which prevented low-income persons from obtaining and using effective methods.

Since the distribution of the most effective methods was controlled by the medical profession and health institutions, it was necessary to look more closely at the way the health system functioned for low-income persons. At that time, the conventional wisdom was expressed in the statement that "the only people in the US who get good medical care are the very rich and the very poor." In the 1960's, Planned Parenthood was reminded (or learned) that the medical care made available to low-income persons consisted primarily of acute, episodic care with almost no opportunity for continuous preventive health services such as family planning*. A large proportion of low-income and minority women had no regular physician during pregnancy but depended on whatever prenatal care and obstetric services were made available by local public health departments and hospitals†; these institutions as a matter of policy rarely offered women the choice of medical contraception. It became clear that the problem of effective contraception for low-income Americans could not be solved unless public policy, and the way in which the health system functioned in the area of fertility control, could be changed. It would be futile to educate low-income persons to request contraception from their typically non-existent private physicians; if they were to obtain effective medical methods, it would be necessary to create a geographically accessible network of clinics and service sites to provide the services at no charge or with heavy subsidy, as well as a means to correct misinformation and inform prospective patients of the availability of services. Such a program could only be established by government and supported by public funds.

This reappraisal within Planned Parenthood coincided in the mid-1960's with the general reawakening of interest in the problems of poverty in the United States. By that time, Planned Parenthood's basic assumptions had been modified sufficiently to enable its leaders seriously to propose a national program to provide modern voluntary family planning services to all low-income persons who needed and wanted them‡‡. The program was politically and technologically feasible, and grounded sociologically in the best available findings of social research.

This focused national program was to pose new issues more subtle than the Catholic problem. One was the accusation, by a small but vocal minority of blacks, that the national program was designed to reduce black fertility and power. Despite the clear evidence that a large number of black women seek family planning services from clinics, and that many black legislators and officials have been in the leadership of efforts to remove restrictions and enact affirmative legislation supporting the program, the charges have received considerable attention from the media and in political and academic circles. Another issue has little to do with family planning per se, but is related instead to differing political philosophies on the role of the federal government in the direction and financing of health and social service programs.

Perhaps the most persistent new political issue has been expressed in the form of arguments over competing approaches to the delivery of health care, such as

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* Cf. Alonzo F. Yerby, "The Disadvantaged and Medical Care," *American Journal of Public Health*, 56:5, January, 1966.

† Cf. Pakter, J. et al: Out of Wedlock Births in New York City, Am J Public Health 51:5, 1961; Shapiro, S., et al: Further Observations on Prematurity and Perinatal Mortality in a General Population and in the Population of a Prepaid Group Practice Medical Care Plan, Am J Public Health 50:9, 1960; and Oppenheimer, E.: Population Changes and Perinatal Mortality, Am J Public Health 51:2, 1961.

‡‡ Cf.: Closing the Gap in United States Birth Control Services, Planned Parenthood-World Population, 1966; and Jaffe, F. S.: A Strategy for Implementing Family Planning Services in the United States, Am J Public Health 58:713, 1968.

"comprehensive" versus "categorical" strategies, or whether family planning can only be provided through general maternal health programs. At the root of these continuing debates are basic differences regarding the appropriate priorities of the US health system. Is the system, for example, to be held accountable for providing basic core services for the many, or is it to continue emphasizing quality care for the few? Is family planning a basic service needed by almost everyone, given the current preferences of Americans? And if it is, and its distribution is controlled by medical personnel and institutions, how is the health system to carry out this responsibility? Underlying the debates is a rarely acknowledged competition for resources among professional groups within the health field. While many health professionals and organizations had been willing to support birth control as a philosophic issue, they were less eager to press for implementation of birth control services for the nation's low-income women because many viewed this step as requiring reallocation of limited health budgets. Many of the arguments beginning in the late 1960's stemmed from fears that family planning would drain resources from existing programs. In fact, priority for family planning was achieved not at the expense of existing programs but by enlarging the health budget.

Health agencies did not respond to the breakthroughs in family planning policy of the mid-1960's with the enthusiasm of newly liberated institutions. The first significant federal initiative came not from the health arm of the U.S. government but from the anti-poverty program administered by the Office of Economic Opportunity. One reason was the competition among professional health interests noted above. But the nature of family planning also played a part: improved control of fertility was known to have beneficial health consequences, but the direct results of family planning primarily were seen as personal and social, not medical; and family planning was regarded by many physicians as tedious, if not boring. Yet distribution of the most effective means of family planning was controlled by the medical profession.

The paradox of relying on the health system to implement purposes viewed as nonmedical persists today and underlies the continuing lack of interest in fertility control of large segments of the US medical profession* and the continuing debate over nonprescription distribution of the pill†. Yet many health institutions modified their programs during the 1960's and devoted some attention to family planning matters; by 1974, 755 hospitals, 1,767 local health departments, and 861 voluntary health agencies could be identified as providers of family planning services. Much of this was in response to the availability of federal funds to finance such services beginning in the mid-1960's. But another factor was the technologic change initiated by the oral contraceptive. Because its mode of action was hormonal rather than mechanical, some physicians became interested for the first time in problems relating to fertility regulation.

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* And the British as well. Cf. Cartwright, A.: *Parents and Family Planning Services*, Atherton, New York 1970; and Russell, J. K.: Planning Family Planning, Lancet 1:310, 1972.

† Atkinson, A., et al: Oral Contraceptives: Considerations of Safety in Nonclinical Distribution, *Studies in Family Planning*, 5:242, 1974; Smith, M. et al: Distribution and Supervision of Oral Contraceptives, Br Med J 4:161, 1974; and The Pill off Prescription, Lancet 2:933, 1974.

The replacement of obsolete assumptions within Planned Parenthood was not a linear process of information and knowledge automatically supplanting bias and misperception. The process was complex, and the new information was never unambiguous. Prodded by its own experiences and stimulated by the findings of US fertility studies, Planned Parenthood by the mid-1960's had developed a different outlook on what was necessary, possible, and do-able. It was an outlook which enabled the movement to take maximum advantage of the emerging political concerns over poverty and population growth, and make a significant contribution to the advances in public policy and programs after 1966. It is possible, perhaps even likely, that broad political interest in poverty and population growth was the critical factor in the policy change. But it seems doubtful that Planned Parenthood would have been effective as an agent of change if it had not substantially altered its outlook.

In this process, technological innovations and changing political relationships played important roles. But the findings of fertility research had the most far-reaching effects. They helped the movement to revise its thinking, determine more specifically what needed to be done, and shape its demands accordingly. They also were used to develop sophisticated quantitative techniques of program planning and development which helped make possible the extremely rapid growth of organized family planning programs after 1968*. Perhaps in no other area of health care have social research findings been utilized so systematically to determine who needs services, who obtains them, and who provides them, and to monitor changes in these critical indicators over time. The studies—principally the 1955 and the 1960 Growth of American Families studies and the 1965 and 1970 National Fertility Studies—presented a detailed picture of the fertility attitudes and practices of the American people over a 20-year period which was invaluable in modifying the outlook of the U.S. birth control organization, in changing public policy, and in guiding action programs to improve the regulation of fertility.

* Cf. Jaffe, F. S., Dryfoos, J. G., and Lerner, R. C.: Planning for Community-Wide Family Planning Services, Am J Public Health 59:1339, 1969; Office of Economic Opportunity, *Need for Subsidized Family Planning Services: United States, Each State and County, 1968* and *1969*, Government Printing Office, 1969 and 1971; Center for Family Planning Program Development, *Need for Subsidized Family Planning Services: United States, Each State and County, 1971*, New York 1973; *Data and Analyses for 1973 Revision of DHEW Five Year Plan for Family Planning Services*, New York 1973, and *Data and Analyses for 1974 Revision of DHEW Five Year Plan for Family Planning Services*, New York 1974; U.S. Senate Committee on Labor and Public Welfare, *Report of the Secretary of Health, Education and Welfare Submitting Five-Year Plan for Family Planning Services and Population Research Programs*, Government Printing Office, 1971; Dryfoos, J. G.: A Formula for the 1970's: Estimating Need for Subsidized Family Planning Services in the United States, Family Planning Perspectives 5:145, 1973.

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Alan Guttmacher, and Family Planning in Cuba, 1966 and 1974

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In September 1965, while attending the World Population Conference in Belgrade, Alan Guttmacher lunched with three delegates from Cuba. One of them, Celestino Alvarez Lajonchere, Professor of Obstetrics at the University of Havana, asked whether he would accept an invitation to address the Cuban National Medical Congress to be held in February 1966. Guttmacher said he would but suggested that two hurdles had to be jumped: "First, Castro has to ask me and second, LBJ has to let me go."*

Although Guttmacher forgot the incident, Lajonchere did not. On December 23rd an official invitation, addressed to "Doctor y Doctora" Guttmacher and mailed in Havana on October 16th, arrived in New York. It was forwarded at once to the State Department requesting permission to go. At that time it was not generally known that the legal rights of citizens to travel had been fully vindicated.† Guttmacher was traveling abroad extensively and it would have been foolhardy of him to imperil his mobility. On January 24, 1966, official approval came from the Passport Division. It was accompanied by several strictures: that travel be on a visa obtained from the Czechoslovakian Embassy in Washington, D.C. or from the Mexican government; that the route be through Mexico City; and that all expenses be paid by Cuba. These limitations were still in effect in 1974. Despite a personal protest, the Passport Division refused approval of Mrs. Guttmacher's travel on the ground that she had no medical mission to perform.‡

Because he had been warned that it might take much time to secure the necessary Mexican exit and reentry permits for Cuba, Guttmacher went to Mexico City 36 hours before his departure to Havana scheduled for Wednesday, February 23. Surprisingly, the permits took only a few minutes to obtain. However, when he went to confirm his Mexico-Cuba reservations, he was advised that the Wednesday flight had been cancelled and that he was now listed for Friday.§

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* Guttmacher's personal notes concerning his trip to Cuba were made available to me by Leonore G. Guttmacher. They supplement conversations with him and with Sally Guttmacher. Some of this information was published in the President's Newsletter #11 of Planned Parenthood World Population of March 15, 1966.

† *Aptheker v. Secretary of State*, 378 U.S. 500 (1964) established the right of US citizens to travel abroad without restriction.

‡ Mrs. Guttmacher could have gone. The Mexican government however, will not issue a reentry permit to a US citizen who does not have US State Department approval. In 1966, this meant that return from Havana would have to be made through Europe.

§ Then, as now, the scheduled flights between Mexico City and Havana were round trips on Monday, Wednesday and Friday, westward in the morning.

Transfer of his presentation in Havana to Saturday was arranged by telephone and he was assured that the Cubans very badly wanted him to come. Guttmacher characteristically used the waiting time to visit several Mexican family planning research and service facilities.

In 1966, Cubana de Aviacion maintained international service to Mexico City, Madrid, Prague and Moscow with a small number of Britannia turbo-props. Problems of maintenance resulted in frequent delays and cancellations. By 1974, this had been improved by the addition of jet aircraft service to Europe by Iberia, Aeroflot, and CSA. Intra-Caribbean service however, was still provided by the same Britannias supplemented by Ilyushin turbo-props.

The 1 p.m. flight to Havana on Friday, February 25th departed at last at 7 p.m. When it landed in Havana it was met by Lajonchere and his staff. Guttmacher was one of the first US physicians, and the first obstetrician, to make an official visit to Cuba since the establishment of the blockade five years earlier. All had hoped that his arrival would be in time for Fidel Castro's reception for Congress delegates that evening but it was past midnight by the time the party arrived at the Habana Libre, formerly the Havana Hilton. Leo P. Krall of the Joslin clinic, who had arrived in Cuba in ample time, had represented the US delegation at the reception. Castro inquired as to Guttmacher's whereabouts and had extended a warm welcome to them all.

The Congress was attended by 3900 of the 7600 registered physicians and dentists in Cuba, and 180 delegates from 25 foreign countries. The session on family planning was one of several simultaneous sessions, and lasted from 9 a.m. to 1 p.m. on Saturday morning. The large room was overfilled, with people standing along the walls and sitting on the stairs. For the first two hours there was a panel presentation in Spanish by Cuban delegates. From 11 to 1 Guttmacher spoke on recent developments. He had prepared an English text which had been translated into Spanish, but the size and enthusiasm of the audience resulted in a decision to speak extemporaneously. Translation into Spanish, a few sentences at a time, was provided by Pedro Valdes Vivó, another Professor of Obstetrics in Havana. Guttmacher opened by saying:

"In this time of bitter tension between different political ideologies, the realization that science, particularly, medical science, transcends such differences lights a spark of hope which I trust for the sake of both our countries will soon be fanned into a bright flame. The voice of science refuses to be silenced by the flexed muscles of conflict. May it always be so." He was given a lengthy ovation.

In the afternoon, Guttmacher toured the scientific exhibits. They consisted of drawings, graphs, and x-rays and focused on public health and newer modalities in diagnosis and therapy. He was struck by the absence of commercial exhibits. He also visited the obstetric service of the National Hospital and heard a clinical report on the hazards of multiple pregnancy based on 123 consecutive cases. Even on so brief a visit to Cuba, Guttmacher managed to indulge his lifelong fascination with multiple pregnancy! Finally, he met with the Minister of Health and other physicians to acquaint himself with the status of family planning in Cuba.

Guttmacher concluded his published comments on the trip as follows:

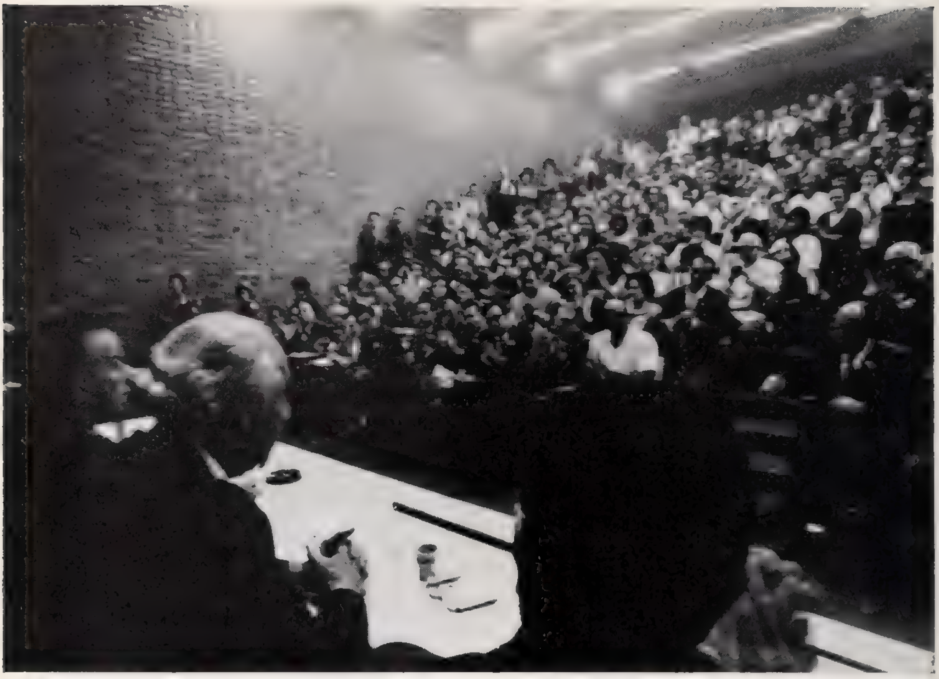

FIG. 1. Alan Guttmacher addressing the session on family planning at the Medical Training Institute, Havana, February 26, 1966.

"Although I barely understood a word, I was fascinated by the oratorical techniques of Fidel Castro who closed the Congress with a two-hour oration in the Charlie Chaplin theatre. He had the audience with him all the way. . . . On Sunday afternoon, attending a double-header, I saw my first home run welcomed in Latin style. The whole bench (each team has 35 regulars) rushed on the field and embraced the slugger. The Minister of Health noticed me in the stands and autographed a brand new baseball which he sent me with his compliments. Perhaps I possess the first and only baseball autographed by a Minister of Health".*

Following this visit, an article about the Congress and Alan Guttmacher and family planning appeared in *Bohemia*, the major Cuban popular magazine (1). Because of the severe shortage of newsprint, there is only a limited number of such journals. They are extensively and avidly read. The comments in this article, including photographs of Guttmacher, are among the few on family planning published since 1959 in a Cuban publication with mass circulation.

After his return to New York, Guttmacher was invited to Washington, D.C. to review his trip with officials of the State Department. During this discussion, it emerged that he was being expected to comment adversely on the state of

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* Guttmacher had confided his interest in baseball to one of his Cuban hosts and was promptly provided with a box seat at the Sunday game.

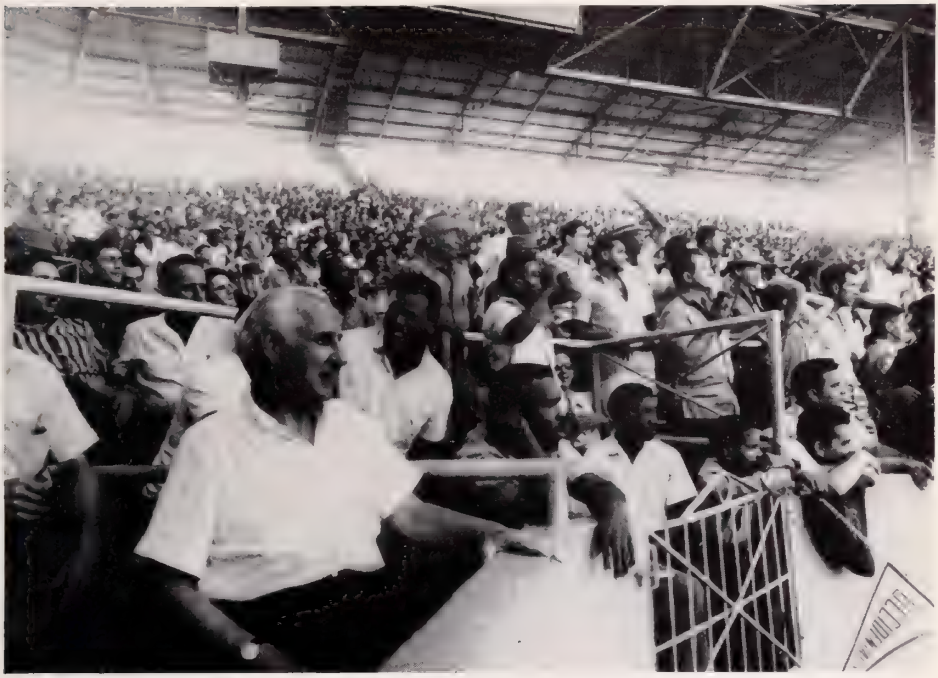

FIG. 2. Alan Guttmacher at the Havana baseball game, February 27, 1966.

medicine in Cuba. Guttmacher was thoroughly apolitical and this offended him. He terminated the interview.

Travel to Cuba, 1974

Some of the extraordinary political conditions attached to Guttmacher's trip in 1966 repeated themselves when my wife and I visited Cuba in February, 1974. Our trip was made at the invitation of the Ministry of Public Health (MINSAP) through the intermediation of the United States Cuba Health Exchange (USCHE). A series of medical specialists and delegations of physicians and health workers has visited Cuba for mutual exchange of knowledge under USCHE sponsorship in the past few years.

The unpredictable irregularities in the mail continue. Our individual invitations from MINSAP were delayed. Our original applications for State Department validation of our passports were lost, and then the Passport Division withheld approval of my wife's travel, although it readily validated my passport. We therefore planned to go to Havana through Mexico and to return to New York through Barbados. As luck would have it, our return flight on Cubana made an unscheduled stop in Santo Domingo where we quite informally changed to a splendid flight to New York on a US flag airline.

We were warned that because of the blockade we could not spend any funds in Cuba including "payment for travel expenses, for accommodations, or for services." In fact the Cuban government provided for all our wants. It was remarkable to go for three weeks without any need to spend money or indeed even to carry any.

I was also warned by the Department of State that "since we lack direct communications with the Cuban government, we cannot extend to American travelers the protection which citizens can expect in a country with which we have diplomatic relations. I would suggest that you be extremely careful during your visit and that you register at the Swiss Embassy as soon as possible after your arrival".* I did so. We found the office located in the basement of the imposing and otherwise unused US Embassy on the Malecon. It is staffed by Cubans who, we were told, are paid by the Swiss with US funds. Guttmacher commented that, "incidentally, I never reported to the Swiss Embassy re protection of life and limb. I felt safer than in New York City." My wife and I had the same feeling in 1974.

Population and the Status of Women

Since the revolution in Cuba, medical care has been considered the right of all citizens and is provided without cost to the individual (2). Certainly since the time of the XIth Medical Congress in which Guttmacher participated, it has been assumed that family planning services would be available from the physicians in the health delivery system. It was therefore inevitable that the government needed definite policies in regard to population growth on the one hand and birth control and abortion on the other.

These policies have emerged in an environment of conflicting social pressures. Putting aside their history, it is possible to describe the factors operative in 1974. The population of Cuba is growing. There have been spectacular changes in health care, which have resulted in a marked drop in perinatal mortality to the point that Cuba now has the lowest rate of any country in Latin America. The adult death rate similarly has dropped because of the elimination of many infectious diseases. Despite the emigration of something like 10% of the population in the '60s, the large upsurge of births in the 15 years following the revolution and the drop in the death rate has more than replaced the emigrants and the population of Cuba now exceeds 9 million.

Unusual among developing countries, Cuba experiences full employment. Since it is a relatively poor country, without surplus foreign exchange, and with no industry producing luxury goods other than cigars, it is not in a position to import a working force. Its international relations with the neighboring islands have not been such as to make this practical. The shortage of workers in Cuba can be expected to continue for at least the next decade. One potential source of workers is the introduction of women to the work force. This has been a policy for a number of years. At the recent Second Congress of the Federation of Cuban Women (Federacion de Mujeres Cubanas, FMC) it was emphasized that the achievement of equality for women, an explicit policy of the government, was in part a matter of fairness and propriety but was also a practical matter in meeting the demands of an expanding society for more workers (3).

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* Letter from the New York office of the Passport Division of the State Department.

Women have been recruited into the work force to harvest sugar cane, previously an entirely male occupation. They have also found employment in the developing industrial manufacture of small household appliances, for example. Women now constitute substantially more than one-third of the national work force.

One consequence of this is that the country recently has established a new maternity law. This not only guarantees to employed women that they will be able to return to their employment after childbearing but also that they will receive full pay during the period of compulsory absence from work. This period of maternity leave is expected to begin at the 34th week, and at the 32nd week in the case of twins, and to continue for a minimum of 12 weeks after the birth of the baby. There are vigorous campaigns conducted in the press and on national television to encourage breast feeding, since it is recognized that this is a substantial factor in the reduction of neonatal mortality from gastroenteritis, a disease which continues to be a major problem.

Women also are expected to take their place in society as professionals. More than half of the students enrolled in medical schools at present are women. It has become difficult to recruit women to attend nursing school.

Inevitably many of these trends fly in the face of the continuing strong traditions of the place of the woman in society. Despite a shortage of yard goods, there are specialty shops in Havana dedicated to the clothing of brides. *Mujeres*, the publication of the FMC, much like the women's magazines in the United States, dedicates substantial portions of its text every month to child rearing, and to household arts. Fidel Castro, commenting to the Second Congress of the FMC, pointed out that in the first popular elections to be held in Cuba since the revolution, which took place in Matanzas Province, women constituted only 7.6% of the nominees and only 3% of those elected. He commented that this demonstrated that the country is still politically and culturally behind (3).

At the present time and for several years, Cuba has experienced a decrease in the number of births and a decrease in the birth rate. This has come to be a matter of growing concern to those attempting to plan for Cuba for the future. They do not wish Cuba to find itself in the position of the industrial countries who have been forced to import workers.

Provision of Family Planning Services

Medical care, which includes family planning services, is provided at the local level by polyclinics and by rural hospitals. In the urban areas, one of these clinics is provided for each group of about four thousand people living in a conveniently defined geographical area. The clinic is staffed with an internist, a pediatrician, an obstetrician/gynecologist, and a dentist. In rural hospitals a similar staff is provided, although in some areas the obstetrician may be replaced by a midwife. Regions containing about 250,000 people are provided with general hospitals and provinces have specialty hospitals as well. In remote rural areas, such as in

Oriente Province, there are medical substations for ambulatory primary care, usually staffed by a single doctor.

Since the supervision of all facilities delivering medical care is vested in MINSAP, there are published, nationally agreed upon standards for medical care (4). It is expected that all physicians will conform to these standards.

Birth control information is provided at all polyclinics and in all rural hospitals. At the present time all of the standard methods of contraception are available. There had been a problem in obtaining oral contraceptives so long as the manufacture of these was concentrated in the United States. Plastic IUD's have been expensive. The earliest IUD's were manufactured in Cuba from nylon suture material, and subsequently were replaced by copper-bearing IUD's which were obtained from Chile. The limitations that have existed have not been based on restrictions of medical information but on economic conditions related to the blockade established by the US government. There are no published data on numbers of acceptors.

Surgical sterilization is carried out quite frequently in the puerperal period. In the rural areas, this has helped to encourage hospital delivery, which has now reached the point where 98% of all births are occurring in the hospital. Sterilization is being offered principally to patients of high parity and is being done immediately postpartum by abdominal tubal ligation. There is considerable interest in laparoscopic sterilization but the availability of this is inhibited by the cost of the instruments. There are no published data on the number of sterilizations.

Cuba has experienced the same numerical trends in elective abortion as those observed in western Europe and in the United States. In Cuba this has been in large part a medical response to the fact that even with the provision of free obstetrical care, abortion continued to be the leading cause of maternal death. The expanding effort to provide women with effective contraception by itself did not appear to be sufficient to eliminate abortion deaths. Therefore, without any change in the basic law, and without publicity, but with universal endorsement, medical establishments have steadily increased the provision of pregnancy interruption. This increase in abortions has not been done to restrict population growth.

The rate of abortion for Cuba increased from 117 per thousand live births in 1968 to 403 in 1972, the latest year for which figures are available.* The abortion rate in 1972 varied from province to province, from a high in La Habana, rural and urban, of 634 to a low of 264 in Oriente Sur. Oriente Sur, a largely rural area, also has the largest number of births and the second highest birth rate in Cuba.

Most of these abortions are done in the first trimester. The basic technique is suction evacuation. Where a medical indication exists, abortion may be done in the second trimester, almost always by the extraovular instillation of rivanol. Of the abortions, 98.8% are done in regional or specialty hospitals, 0.8% in rural hospitals, and 0.4% in the few polyclinics provided with inpatient facilities.

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* These rates are calculated from interruptions reported in: Cuadro No. 12, Obstetricia, 1972. Dirección Nacional de Estadística, MINSAP, La Habana, April 1973 and from live births reported in: Tabla No. 5, page 46 in: La Atención Materno Infantil y La Reducción de la Mortalidad Perinatal en Cuba, by Cabezas Cruz, E., Duyos Gato, H. and Rojas Ochoa, F., prepared for 30th Anniversary of the Mexican Institute of Social Security, January 1974. The figures are subject to minor revision and include minor inconsistencies.

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Recruiting the Uncommitted Leader for Family Planning

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JOHN C. COBB, M.D., M.P.H.

> "War is much too serious a thing to be entrusted to the generals" *Georges Clemenceau*
>
> "The population problem is much too serious to be left to the experts." *The Authors*

The problem of population growth, especially in the developing nations, is so overwhelming that it would seem reasonable to gather our most capable experts to help solve it. But who are the experts: demographers, sociologists, economists, health educators, public health nurses, obstetricians, or public health physicians? Each of these can make a contribution to its solution, but in the final analysis, the problem is so large and so complex that there probably are no experts and certainly no single class of experts, to whom the problem can be entrusted solely.

In 1965, one of us (T.S.M.) placed a letter to the editor in the *New England Journal of Medicine* suggesting that one or more institutions in the United States establish a program of short-term courses about the population problem for physicians from the developing nations visiting or studying in the United States (1). They would be accepted regardless of specialty if they certified they definitely were returning home. It was felt that through such a program interested but uncommitted physicians could recognize the importance of the population problem and would be encouraged to direct their activities towards its solution. It was our thesis that if enough capable individuals recognized the enormity of the problem and learned what others have done, they would be motivated to find a solution.

Subsequently, in 1966, one of us (J.C.C.) set up a short course on population and genetic problems at the University of Colorado, with funding from The Population Council, for attendance by third-world physicians who were in the United States for studies. There was a sufficient number of applicants and we were eager to get additional funding for more such courses.

Many agencies were approached, but funding for this type of short-term course was not available until Dr. Alan Guttmacher was contacted and became an enthusiastic supporter of this idea. He urged us to go forward. In July of 1972, with his support, we were able to obtain funding from Family Planning

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International Assistance of Planned Parenthood-World Population, which in turn received support from the Agency for International Development. The funding included money for the course itself, as well as living expenses and round-trip transportation costs for the participants. Those coming from overseas were paid their round-trip transportation from port-of-entry into the United States. In October of 1972, the first one-week course began with the optimistic title, "Solutions to the Population Problem." Of course, we recognized that we could offer only partial answers.

Course contents

The course includes presentations regarding the seriousness of the population problem. We have utilized the Plato projector system developed by the University of Illinois to display computerized demographic data, to emphasize the catastrophic consequences of present trends. This is followed by a description of existing contraceptive technology and the various ways in which contraceptive technology has been delivered to the public, including organized family planning programs and the use of commercial channels. In addition, the medical benefits of family planning are presented as well as the social, cultural, and religious factors which affect the acceptance of family planning. Finally, the problem of large numbers of illegal abortions throughout many parts of the world is discussed, and the difficult moral question, "Should abortion be made legal?" is fully aired. All sessions are presented with the maximum possible time for discussion. The range of opinions as well as new ideas elicited from the participants has been truly impressive.

During the course, the participants are informed about where to apply for financial support of family planning programs. They are given the addresses of family planning organizations in their country and the addresses of all previous participants in the course from their country, so they can become associated with groups who have similar interests and objectives. They also receive periodic mailings of current publications in the field of population control.

Course objectives

It is believed that the physicians attending such a course will use the information gained in several ways. First, they can use the technical information regarding family planning in their practice, and the experience of programs in other parts of the world in the development or improvement of programs in their country. Second, some may engage in research or evaluation of contraceptives or programs. Third, a significant proportion of these physicians may be interested in exerting political influence to alter their countries' policies or programs in the area of family planning or birth control. Physicians in the developing nations frequently are engaged in politics, and the political influence of such a course could be considerable. This influence may be particularly helpful in implementing controversial but potentially productive measures such as: much more extensive use of paraprofessionals with increased responsibilities; widespread distribution of oral contraceptives by community workers or various types of commercial outlets with minimal medical control; and possibly the liberalization of restrictive abortion laws.

Numbers and characteristics of participants

Through 1974, we have presented 12 one-week courses with a total enrollment of 375, with an additional optional week of practical training for 48 participants. The largest number of participants, 122, has been foreign physicians from the developing nations who came to this country at their own expense and who at the time were engaged in various types of training, usually in residency and fellowship positions. These physicians have been notified by direct mail. Initially, we utilized the American Medical Association lists of foreign medical graduates and later we utilized the lists of the Council of Foreign Medical Graduates. For this group in particular, the course has been an eye-opener regarding the seriousness of the population problem and programs currently underway in their country, as well as alternative approaches used in other countries.

When Mexico changed its national policy in favor of family planning, we decided to invite English-speaking physicians currently practicing in Mexico (without any restrictions regarding their field of specialization). We also notified physicians in the entire Caribbean area. In order to reach English-speaking physicians who are motivated to stay current in medicine, we obtained from eleven different medical journals published in the United States their distribution lists in these countries, and sent notifications to each address on those lists. This method, which was suggested by Dr. Warren Hern and only used for the last seven courses, resulted in 99 physicians from Mexico and the Caribbean area attending the course. Since our regulations require that the participants from these countries pay their own travel expenses to the US border, we find we have selected a group of physicians with a higher than average motivation. The motivation is further reinforced by the fact that most of the Caribbean countries and Mexico have only recently begun their family planning programs and many of their physicians are eager to learn "what to do." We feel that the same technique of utilizing journal distribution lists could be used in any country to find intellectually active, interested, but uncommitted physicians to attend courses regarding the population problem.

A third group of 81 physicians who have attended the course have been sent to the United States by governments or foundations for various types of training. These fall into two main categories: 1) those who are here for long-term training, usually in some field other than population; and 2) those who are already working in the population field and are here for short-term training, or visiting various centers. While physicians in this last category fall outside our original objective of recruiting the uncommitted physician, their participation has been very productive. They have helped the course by their enthusiasm and by presenting material on practices and programs in their countries. Many of them have told us that they have benefited from the discussions and learned about new ideas that they want to try in their country.

A fourth group of physicians who have attended the course are 44 American missionary physicians who work in the developing nations. Most of them have been Protestant missionary physicians, but one was a Catholic priest and one a Catholic nun. Obviously, these Catholic leaders didn't agree with us on all issues, but they both stated that the exchange of viewpoints was extremely valuable.

A small group of 17 physicians who reside in third-world countries other than Mexico and the Caribbean area have attended during a personal visit to the United States. Most of these learned of the course through notifications to missionary physicians, but a few learned of it from friends in this country. These physicians appeared extremely capable and motivated.

Finally, there have been 12 nonphysicians, i.e., nurses, medical students, health educators, social workers, and administrators, who have attended. While some of the presentations on contraceptive technology may have been too complicated for them, they readily understood the material on the extent of the population problem and the issues and problems involved in instituting birth control programs, as evidenced by their enthusiastic contribution to discussions of these issues.

The number of participants who have attended these 12 one-week courses, 375 as of this writing, compares quite favorably with the number of participants who have received population training at Schools of Public Health or other training programs in the United States. We believe that attendance has been enhanced by the brief time required for this course. The brevity of the program (one or two weeks), while leading to difficulties in presenting all the material, or permitting discussions to be as complete as we would like, makes it possible for the capable but busy physician to take the time off to attend. It may be the only way we can reach these valuable, active individuals, who are likely to have great influence on the decision-making process in their own countries.

Preliminary evaluation

In November, 1973, a short questionnaire was sent to the 183 participants in the six seminars held between October 1972 and October 1973. This first attempt to evaluate the long-term impact of the course included five questions pertaining to the respondent's practice and his attitudes regarding family planning.

A low return rate (34%) does not allow us to assume that the data are representative of the universe of participants, and the information obtained from this first questionnaire should be seen only as applying to those participants who returned the questionnaire.

At the time of our survey, a good number of respondents were still in the United States some because early recruiting techniques were not sufficiently developed to screen out applicants who were unlikely to return to their countries soon after the seminar, and others because only a month or two had elapsed since the last seminar. However, the data demonstrated that the rate of participants returning to their country increased significantly for those attending later seminars.

Table I gives the results of our survey. Column A gives the question as it was

TABLE I

A.	B. All Respondents	C. Respondents Who Returned Home
1. "Are you now doing work in the field of family planning?"	Yes: 57% No: 43%	Yes: 72% No: 28%
2. "Have you been discussing the family planning and population problem with your colleagues or influential people in your community?"	Yes: 83% No: 17%	Yes: 88% No: 12%
3. "Do you now feel our course was generally helpful to you?"	Yes: 100%*	Yes: 100%*
a. Very helpful	56%	50%
b. Somewhat helpful	44%	50%
c. Not very helpful	0%	0%
d. Not helpful at all	0%	0%
4. "To what extent do you believe the course has altered your *thinking* about family planning and population control?"	Yes: 68% No: 32%*	Yes: 71% No: 29%*
a. Significantly	35%	31%
b. Moderately	33%	40%
c. Very little	25%	19%
d. Not at all	6%	10%
5. "To what extent have you altered your *activities* in the field of family planning and population control as a result of the course?"	Yes: 50% No: 50%*	Yes: 62% No: 38%*
a. Significantly	17%	18%
b. Moderately	33%	44%
c. Very little	29%	26%
d. Not at all	21%	12%

* "Yes" includes categories a and b.

stated in the questionnaire. Column B shows the response of all 63 persons who returned questionnaires. Column C includes the results of only those participants who had returned home at the time of the survey. In all cases but one (question #3), the course seemed to have a higher degree of the desired effect upon the group who had already returned home. A majority of all respondents, 57 percent, report that they are now doing work in family planning. Unfortunately, we have no data on the number of participants who were doing work in family planning before they attended the seminar. It is significant, however, that 72 percent of those who have returned home report they are working in some area of family planning. Of those that have returned home, and therefore most likely to be in positions of implementing their training, almost two-thirds (62 percent) reported that the course had an effect on altering their activities in the field of family planning.

A great majority of respondents provided some detail about the types of activities in which they now were engaged. For example, a doctor in Taiwan stated that his attitude toward permanent sterilization has changed. "In past we did operations on those women who had three or more children, but now we do it with two children if the mother requests it." This altered viewpoint seems typical of the group who previously had been involved in family planning, and whose attitudes and practices had changed as a result of the course.

The minority who stated that the course had very little or no impact on changing their attitudes or practices generally fall into the categories of those still in the United States, those in specialities unrelated to family planning, those working in countries where family planning is illegal, and those, the largest segment, who were already working in the area of family planning and committed to its value.

Some participants who felt their activities had not changed, since they practice in fields removed from family planning, provided details which disclose the opposite. A Mexican neurologist, for example, stated that his "activities have not been altered . . . I only have had conversations with fellow doctors, patients, relatives, etc., trying to convince them of the importance of family planning. . . . " This doctor was typical of many in that it gave him a greater awareness of the problem. His desire to communicate it to others can be judged as a significant impact of the seminar. He stated " . . . it made me especially conscious of the tremendous demographic, economic and social problems that my country will have to face in the future, unless we try to avoid them now." He is also typical of many in his statement that "I wish I could be able to show it (the demographic projections) to my colleagues and countrymen, so they become aware of these problems as we did."

Another statement along these lines was by an Indian. "The projections of population are horrifying . . . I would suggest that the staff should visit India and other developing countries with their slides and run short-term seminars there. Those of us who visit abroad are already, to some extent, aware about the problem. If, on the contrary, the team could come to India, they could influence a large number of people."

It is obvious then, that while many physicians technically have not been active in family planning, the data indicate that the course has had an important influence on their attitudes toward the problem and in moving them to proselytize.

Many who have returned home report that their practice also has been influenced by the seminar experience. For example: "I returned to Lebanon (and) joined the Child and Mother Welfare Society and I work one day a week in one of their Dispensaries . . . I take advantage of the opportunity to tell parents about methods of FP. . . . I am planning for the future to meet with the Ladies of the Society to urge the institution of a FP program—the task is enormous because everything has to be started from the beginning. But I think there is a real need for it."

Extension of the Concept

This type of approach, attempting to recruit the "uncommitted physician," could also be used to recruit the "uncommitted but capable person" from any field. Economists and government planners need to recognize the impact of population growth on any development plans and act accordingly. Businessmen must recognize their potential contribution in selling condoms, vaginal spermaticides, or oral contraceptives in regular commercial channels, and in encouraging company employees to practice family planning. Teachers could realize their potential role in providing basic "population education" for their students (and, if the local culture permits, also discuss reproduction and contraception). Military leaders should understand that teaching contraception to the young men in the Army is one effective way of spreading the idea to men in all strata of society who are in their reproductive years. The "unemployed wives" of various types of leaders may recognize that they can play an important leadership role in furthering the birth control movement, as such women have done in many countries. Journalists can realize their potential role in educating the public. There is something that persons in almost every field can do to help solve the population problem if they are motivated to do so by learning of its enormity and are introduced to its possible solutions.

Large numbers of these potential but uncommitted leaders come to western countries every year. In the academic year 1970–71, there were 145,000 foreign students in American universities; 75% of them were from the developing nations (2). Furthermore, there were approximately 569,000 visitors to the United States in 1970 from the developing nations as estimated by the number of visas issued (3). There must be similar numbers of third-world students and visitors in other developed countries. Among such a large number of individuals there probably are many persons with a social conscience who could be interested in learning what they can do about the population problem. Furthermore, the proximity of Mexico and the Caribbean countries to the United States or North Africa to Europe makes it economically feasible for participants from such countries to come for short-term courses. Therefore, it would seem reasonable to offer short-term courses in population control to such persons.

Notification of this group could be accomplished by using Immigration Service records and by contacting the foreign student advisors in Universities. The Immigration Service could present short-term visitors with a notification of the course upon entry to the country. Furthermore, distribution lists of various types of journals and magazines in geographically close developing countries could be used to send notifications of the course. By trying various methods, an effective way of contacting these persons could be found. Undoubtedly, only a small percentage of the individuals notified will want to come, but those who do participate are likely to be socially conscious innovators or leaders with a high degree of motivation. These people, then, would provide a valuable nucleus for broad attitude change in their home countries.

Summary

The unprecedented problem of rapid population growth is most severe in the developing nations. In order to help solve this problem, the University of Colorado, with encouragement and assistance from Dr. Alan Guttmacher, gaine

the support of Planned Parenthood-World Population and the Agency for International Development to establish one-week courses regarding the population problem for third-world physicians who are temporarily in the United States, or who live close enough to the United States to come to this country with relatively little transportation expense. It is open to all physicians from the developing nations regardless of background. In the first two and one-half years, these courses have been well attended and appear highly successful. Therefore, it is proposed that the concept and support be extended to permit one or more educational institutions in the United States to offer similar short-term courses for any third world student or visitor who is studying or working in fields other than medicine. This hitherto untried approach should help find socially conscious innovators and leaders who could be shown how to use their capabilities toward alleviating the population problem of their countries.

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Financial Assurance for Reproductive Health Services

CHARLOTTE MULLER, Ph.D.

Insurance coverage for reproductive health care provides not merely a means of paying for service but also a means of sustaining a resource supply and of making it more probable that women will seek timely care and achieve optimal health results. A similar purpose is served by other social mechanisms for financing health care. Because of these implications, the improved distribution of adequate coverage among women of childbearing age is a significant concern of reproductive health policy.

Private Insurance

So far as current private insurance is concerned, the link between the individual and the insurance system is most often membership in a group, usually at the workplace, or a dependent relation to a group enrollee. Group coverage in 1972 accounted for almost three-fifths of insurance company enrollees and for the bulk of enrollees in Blue Cross-Blue Shield and independent health insurance plans (1).

Despite the high level of participation of women in the labor force, they are less likely than men to hold direct entitlement to health benefits. Of 46 million full-time workers in April, 1972, 74 percent of the men were covered compared to 61 percent of the women. This is partly due to the fact that men are more likely to be found in high-wage industries and in better-paying occupations, and partly also to waiting periods based on length of employment, with women less likely to qualify. But even within each length-of-service category, a higher proportion of men than of women have coverage.

Many married women who are in the labor force, and of course many who are not, receive health benefits through their husband's employment. Among married men, 76 percent are covered and 90 percent of these have some coverage for dependents. This would mean that 68 percent (90% × 76%) of wives of men in the full-time labor force, or 25,512,000 women, are covered through their husbands. This leaves 2,834,000 married women (wives of men with no dependent coverage) who are not covered through their husband's job, and 8,555,000 wives of noncovered married men, or in all 11,389,000 women with husbands in the full-time labor force but no coverage as wives. As only 57 percent of married women workers are directly covered, there are 5,763,000 women (the remaining 43 percent) whose only group coverage would have to be through their husbands. Because in some households both spouses are eligible as primary enrollees it cannot be assumed that of the almost six million women in this dependent state as many as 68 percent are covered under their husbands' policies. Hence the number of married women lacking coverage almost certainly exceeds 1.8 million.

From the Center for Social Research, The City University of New York, N.Y. 10036.

Of single women (never married), 70 percent or 2.8 million women are covered for health benefits, and of widowed or divorced women, 67 percent, or 2.4 million women, leaving 2.6 million in the nonmarried group uncovered. The total of uncovered women, single and married, is thus at least 4.4 million and possibly closer to 8.4 million.

Coverage figures by age show that direct coverage for women is lowest in the age groups under 25 years (59 percent) and 35 39 years (54 percent)- ages which are of interest because of the possibility of high-risk pregnancies and the need for fertility control in both of these groups, and the frequency of childbearing in the younger group (2).

Figures on commercial insurance coverage of reproductive health care are not as detailed as one would wish. A 1973 survey of the group health insurance policies written by major insurance companies is in conformity with the labor force coverage data from the Social Security Administration: most employees had maternity coverage for themselves or their spouses, providing a benefit for hospital care and an allowance for the attending physician (3). The amount of the benefit is indicated by data from a 1970 survey: more than two-thirds of the covered employees have benefits of under $500, and in the smaller groups, a similar percent have benefits of under $75.

Some additional benefit is derived from major medical features, provided, however, that maternity is not excluded and that the benefit is not restricted to specified severe complications. Such restrictions would prevent application to women with tuberculosis, diabetes, or other conditions who need additional services during pregnancy and at delivery. Sixty percent of "cases" (signed-up groups) have supplementary major medical policies, and 88 percent of these have $15,000 or more as a benefit maximum. Another 29 percent of "cases" have comprehensive major medical; 97 per cent of these having a similar maximum (4). These figures provide a base, if used, for effective maternity coverage.

Factors in Adequacy

Features of insurance policies that affect the adequacy of reproductive service coverage include:

1. Specific inclusion of the following areas of service: abortion, sterilization, family planning, normal delivery (including prenatal and postpartum care), complications of maternity, infertility, laboratory and x-ray. Early pediatric care is also conceptually a part of the service package.
2. Benefit levels compared with market charges for each of the above.
3. Eligibility of and benefits for "children," a category now extending well into the twenties in many groups if parental support is received, students, and unmarried (including previously married) female employees or individual subscribers.
4. Terminal liability if a member leaves the employee group while pregnant.
5. Waiting periods.

A comprehensive presentation of the extent to which each of these features approaches the ideal of total protection for women in the reproductive ages would be too lengthy to attempt here. Data from Blue Cross and Blue Shield national organizations (5) will be used to illustrate the variable adequacy of existing provisions. Abortion coverage has increased (within a maternity indemnity) but some Blue Cross plans do not cover out-of-hospital service and others offer it as an optional rider. Sterilization is usually covered but a few plans impose eligibility limits or a waiting period. Maternity complications may be covered without qualification, or with restrictions such as: cesarean section—cash amount or days limited; ectopic pregnancy—excluded. Normal delivery is covered for a varying number of days in hospital. In some plans there is a deductible; in others, an indemnity (flat) allowance is provided, which may be as low as $75, or $15-20 a day (1971 figures). Nursery costs generally are covered during the covered during the mother's stay, but the daily amount may be small compared to prevailing charges.

Both inpatient and outpatient x-ray and laboratory service are frequently involved in maternity and other fertility-related care. Most plans have coverage when outpatient surgery or an inpatient admission occurs, but there are a few cases of partial coverage or total exclusion. Infertility is covered as an ordinary medical condition if hospitalization occurs, but is usually not mentioned specifically.

Ambulatory benefits under Blue Shield are more restricted than would be desirable for comprehensive fertility care. Prenatal and postpartum service is usually considered to be part of maternity, but preventive services such as contraception and well-infant supervision are not part of basic coverage. Financial access to infertility care also suffers from inattention to ambulatory features in policy design. Riders are offered for extra services to groups that can and will pick up the extra costs. Family membership is required for maternity benefits in most plans but the group can secure single-person or dependent-child coverage at extra expense through riders. Abortion coverage may be added in the same way.

A bill requiring "complete maternity insurance coverage" to be offered in private insurance contracts regardless of marital status or age of either the member or dependents was introduced in Georgia in 1974 (House Bill 1362). It applies to hospital and medical services, and extends to cash disability (accident and sickness) policies on both a group and an individual basis. Deductibles and coinsurance may be allowed only if usual and customary charges are met to the same extent as for other surgical procedures. The insured may elect partial instead of full coverage. Several other states report bills touching some or all of the points in the Georgia bill in the 1973 or 1974 legislative sessions (6).

A method of measuring adequacy of insurance for fertility-related health care has been developed, which relies on 1) statistical data indicating the probability of individual categories of service being required in a population of 1,000 women in fertile age groups, 2) market price information for physician and hospital care, surgical procedures, anesthesia, drugs, and devices, and 3) comparison with specific benefits under an insurance contract. This method was applied to the

Federal employees' high-option plan using demographic and medical care market information for Jacksonville, Florida, and a figure of 73 percent adequacy was derived (7).

Delivery of some fertility-related benefits (abortion, sterilization, infertility) will depend not only on financial provisions but also on specialized capabilities of local hospitals, laboratories, and physicians, and on hospital rules specifying conditions under which patients will be admitted for sterilization, etc. Additionally, the range of available methods of contraception, sterilization, and abortion may be dependent on the local level of practice, representing diffusion of medical technology. This will influence the adequacy of insurance that is held, as costs will be affected. Medically, too, safety and outcome of care will be affected. Hence there is need to consider as a joint planning responsibility the financial, institutional, and professional education aspects of effective assurance of service.

Public Sector Responsibility

The precedent for Federal aid to maternity care was set in the Sheppard-Towner Act of 1921, which lasted nine years. Its pattern of matching grants-in-aid to states was copied in the Social Security Act of 1935, which through its maternal and child health grants subsidized support of prenatal clinics, care of premature infants, and other purposes. The Emergency Maternal and Infant Care program during World War II applied Federal funds to obstetric care of servicemen's wives, and was distinguished by its quality standards for physicians and hospitals (8). Since 1956, the successor program, now known as CHAMPUS (Civilian Health and Medical Program of the Uniformed Services), has offered complete maternity care in civilian and military facilities without a means test and with minimal cost sharing (9). In 1963, Congress authorized Maternal and Infant Care project grants to assist in dealing with high-risk pregnancies.

For the most part, maternity services have been provided to public sector patients through the welfare system for many years and such services, like all health care for the poor, have varied in extent and quality between states and localities and have gone up or down over time in response to fiscal exigencies and to congressional commitment to federal financial participation. Consequently, many pregnancies among low-income women have been unsupervised until the last trimester and even until the onset of labor. The percent of low-income women with live births who saw a doctor in the first trimester was 42 percent in 1953, 67 percent in 1958, down to 58 percent in 1963, and, following Medicaid, up to 71 percent in 1970 (10). (Low income was defined as under $4,000 in 1963 and under $6,000 in 1970.) In New York City in 1970, the percentage of live births with late, no, or not stated prenatal care among *all* income groups was 34.5 percent for Brooklyn, 33.5 percent for the Bronx, 29.5 percent for Manhattan, 21.2 percent for Queens, and 15.0 percent for Richmond—29.8 percent for the city as a whole (11).

The government share of hospital costs for maternity care, as derived from expenditure figures net of Medicare and certain other programs, is estimated at about $760,000,000, or 62 percent of the cost of births among women at incomes under 200 percent of the poverty level. A companion estimate (derived somewhat differently) for physicians' services credits the government with about 25 percent of total expenditure for low-income mothers' births. Together these public sector contributions make up about one-half of the total average cost per birth in low-income groups. The programs through which the cash flow occurred are public assistance vendor payments, maternal and child health, and general hospital and medical care (12). The estimate is probably conservative because of the omission of CHAMPUS, and even more so because CHAMPUS provided care equivalent to private sector care.*

The specific contribution of maternal and child health programs to reproductive health services is limited. In 1972–73, at all levels of government these programs expended $455.3 millions; as a large share of this sum went to health services for children at various ages, a relatively small portion of the financial requirements of maternity and early pediatric care among the poor was met from this source. If this dollar total is considered in relation to perhaps 1,000,000 live births among the poor and near-poor and about 5,000,000 children under 5 years of age at this economic level, it appears quite modest.† The main public source of health care including maternal and infant care is Medicaid, estimated to have reached at best one-third of the poor.

Family planning acquired attention in its own right because of the relation to poverty, population, and maternal and child health. Federal financial responsibility for family planning was assumed in 1964, with a grant from the Office of Economic Opportunity. Family planning was included in Federal sharing under Medicaid, Aid to Families with Dependent Children, and maternal and child health programs, and beginning in 1967 was a mandated service for public assistance recipients. The adequacy of the appropriations, never complete in terms of numbers of the poor and medically indigent populations, has varied with federal welfare policy. Furthermore, specific provisions restrict the population coverage: a low-income ceiling for eligibility, exclusion of women with children who are living with husbands and of single or childless married women, prior certification by a welfare department before service may be rendered, etc. Consequently, in recent years few patients in subsidized programs were financed by Medicaid. Prohibitions on use of public funds for abortions, or unwillingness of local hospitals to perform them, further restrict the effect of public money in opening up the reproductive services market to the needy. Genetic counseling and infertility are unevenly and inadequately available to public sector clients in many localities. A serious limitation is the lack of outreach in public prenatal programs, which undoubtedly contributes to the late date at which the first contact with health care in pregnancy so often occurs (15).

Although cost-benefit analysis has been favorable to further public investment in fertility-related care, substantial present spending is unavoidable if future benefits are to be reaped and program gaps filled.

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* All Department of Defense hospital and physician expenditure in 1972–73 was estimated at $1,816,000,000 (13).

† Based on about 3,200,000 live births in 1972 and about 17,000,000 children under 5 in 1970 (14).

National Health Insurance

As the United States moves closer to a system of national health insurance in some form, the opportunities for assuring adequate basic reproductive health care for women will be derived from the combined effect of provisions of an initial enabling act and any later amendments enacted by Congress. Accordingly, some comments on recent proposals may be pertinent.

Proposals for national health insurance tend to contain certain provisions specifically affecting fertility-related health services, but additional effects of a given proposal on these services must be inferred from general provisions about who is covered, benefit scope, etc. Catastrophic insurance proposals have little to offer for normal maternity, ambulatory prenatal, and family planning services, and health supervision of infants of reasonably good health status at birth. In a catastrophic plan, coverage may come into play in connection with a difficult pregnancy or delivery, serious complications of an abortion, or a live birth associated with congenital abnormality or low birthweight. However, large deductibles and copayments limit the number of cases that would qualify for catastrophic benefits.

So far as noncatastrophic, or general, health insurance bills are concerned, the effect on reproductive health services will depend on a number of features jointly considered. Exclusion of preventive care (or limitation to illness care) eliminates prenatal, postpartum, and most family planning services for women. Whether abortion and sterilization also are rejected as preventive would appear to depend on administrative policy and the position taken by doctors signing claims. The exclusion of preventive care also rules out immunization in early infancy, well child supervision, and anticipatory guidance. Infertility services are likely to be viewed as illness-related, and hence included. Alternatively, preventive services could well be included but their provision constrained by limits on the number of visits per year or per condition or on the number of hospital days, as well as by patient cost-sharing. Reasonable limits on units of service could no doubt be tolerated within customary family planning, infant, and prenatal protocols, but for the unusual case, requiring extra care, much depends on whether major medical or catastrophic supplementation includes fertility care at all and, if it does, whether it embraces a broad range of conditions. For most patients, coverage of drugs and devices may be of little moment in influencing contraceptive practice, but there will be some for whom any copayment rule or exclusion of a service from coverage tips the balance against a particular visit for medically supervised contraception or closes off part of a desirable range of choice of method. Another legislative feature that is pertinent to reproductive care concerns orientation of payment methods and forms of practice qualifying as providers. Fee reimbursement tends to favor rapid processing and use of those contraceptive methods that do not require a prolonged medical examination or counseling. As an offset, it provides an incentive for frequent and adequate patient visits. Reimbursement standards would have to recognize these potentials by honoring only visits within an acceptable protocol for a total (uncomplicated) pregnancy or a year's fertility control or infant care schedule.

A number of features relating to eligibility for coverage based on the workplace affect women differentially. The waiting period after hiring for initial eligibility either as a full-time or part time employee may work against the needs of women, who are more likely to be "new hires" and to hold part-time jobs. The continuation of coverage after termination of work is particularly important because of the possibility of a pregnancy-related separation. This feature also affects female dependents of employed men who lose their jobs. These points are of special concern because successful contraception depends on continued adherence to a method. Another work-related feature is employer-sharing in premiums. If, as in one recent proposal (the Packwood bill), benefits above a minimum level are to be financed solely by the workers, comprehensive reproductive health services cannot be assumed to be available so long as they are added as optional features. Furthermore, if employee participation in basic coverage is voluntary, some workers will find having to pay part of the premium a deterrent. If a plan is fairly comprehensive but the employer is responsible for offering the coverage, a high-risk candidate may be denied employment for fear of increasing premium costs. For women, this could mean being limited to employers who offer more restricted benefits and thus facing pregnancy with poor protection.

The technology of future health care is affected by legislative clauses implying or stating approval of modes of practice that recognize and encourage physician assistants to perform core tasks in family planning, prenatal checkups and normal delivery, well child supervision, and primary diagnosis and treatment of the sick child according to protocols instituted by physicians. Task delegation is one of the major possibilities for assuring mass delivery of health services. For it to enter into insurance, payment must be specifically authorized to providers employing assistants under suitable standards of professional discipline. Payments for institutional arrangements and facilities such as remote TV links may require special language and departure from a fee-per-visit basis.

Adapting Insurance to Changing Clinical Standards

Fertility management by individual couples in the current social environment has implications for maternity services accepted as customary and the consequent need for insurance. As each pregnancy is more likely to be highly valued than previously, liberal admission to hospital if anything suggestive of risk occurs, commitment to fetal monitoring before delivery, use of cesarean section, and intensive service at the time of delivery and for high-risk neonates are expected to contribute to increased financial requirements for maternity care. To the extent that regionalization develops—with high-risk pregnancies concentrated in adequately serviced and equipped hospitals having neonatologists, experts in perinatal medicine, etc.—insurance policies, to adapt to these changes, will have to cover the event of transfer to such institutions, will have to use language to apply to the extra services that may be needed, and will have to create the major medical entitlement to match the financial burden. In general, insurance language should be broad so far as techniques are concerned, since rapid change in technology can make well-intentioned phrases inapplicable.

It is believed that adequate care for women in childbearing years and at menopause is preventive of later morbidity and death. Insurance can contribute to this for example, if diagnostic dilation and curettage, performed in the doctor's office with the aid of aspiration techniques instead of in-hospital, is included, and if Pap smears, an ambulatory service, are in the benefit package. Refusal to honor claims if delivery is in a hospital with inadequate volume or substandard conditions might force needed upgrading in some communities. This too would be preventive.

Cash Income Benefits in Pregnancy

Pregnancy disability coverage is an insurance issue related to assuring optimal reproductive health. The general record of the handling of pregnancy-related absence from work until recent years was that women frequently were compelled to take maternity leave for a period extending several months after delivery, sometimes starting early in pregnancy, or to terminate employment. Indeed, in some school systems and other employments there were no jobs for married women at all. Women rarely were permitted to file for ordinary sick benefits for a medically relevant period before and after delivery. Commonly, all health insurance benefit entitlements would be absent during the involuntary leave. Whether they ended on the enforced severance from the job would depend on terminal benefit provisions under state insurance law. From the health point of view, this uncovered state would jeopardize receipt of timely maternity services. Furthermore, an incentive was set up to conceal pregnancy owing to fear of the economic consequences. Apart from resultant failure to use industry-based health plans to sustain pregnancy care, the concealment also would stand in the way of desirable adaptation of job conditions for the protection of the pregnant woman.

Employers often used medical and social considerations to justify their refusal to honor pregnancy as a medical disability. Although the absence of the mother from the home in the child's infancy, and the mother's double tasks if she did work, clearly could be detrimental to infant development, emotional health, and maternal welfare and were regarded with disfavor by most women, the attitude of employers did not assure the presence of the mother at home in the event of economic necessity nor a tranquil emotionality. In cases where welfare assistance replaced earnings, nutrition and medical care may have suffered. Loss of job seniority undercut the earning trend of the employed woman and the opportunity for those aspects of health maintenance that depend on cash. The employed father was not necessarily able to sustain the household economically if unemployment, death, or disability struck. The merits of the severance of women from employment during pregnancy as a universal rule were not well-documented but were treated as self-evident. Some jobs were obviously inadvisable, others easily tolerated into late pregnancy. Often public acceptability and exposure of school children to the sight of pregnancy were cited as factors. Ambivalent views about female sexuality are reflected in these policies. In one university system, a woman professor was obliged to inform the college president as soon as she knew she was pregnant! Meanwhile, many European countries recognized pregnancy with maternity benefits in both cash and health services.

With the Equal Employment Opportunity Act and Federal guidelines, it is viewed as a violation of equality in the labor market for health and disability benefits to contain discriminatory provisions relating to maternity.* Court cases upheld the right of women to medically related pregnancy leave (17), but an adverse ruling was handed down by the Supreme Court in 1974. However, litigation is not ended by any means. It is obvious that many employers will not extend the coverage without being compelled to do so. Unions that have failed to set up pregnancy coverage on an equal footing with other conditions causing absence from work and use of medical and hospital service in their health and disability plans established under collective bargaining also have been faced by suits from organizations of female employees.

Meanwhile women often use sick leave, annual leave, and unpaid maternity leave to maintain their labor market connection during and after pregnancy.

Pregnancy disability coverage should not interfere with the decision of women to absent themselves from jobs for extended periods of child care and enjoyment of the parent-child relationship. But there will be some families where the parents decide the allocation of parental and economic duties according to their particular needs, and this results in the father taking on himself a large share of nurturance. Paternity leave is an open recognition that this arrangement will be sought. The employed mother is able to retain health benefits for herself and her infant or to qualify as her husband's dependent and is not involuntarily deprived of these entitlement options through loss of her own employment. Retaining status in the labor market may commend itself to many women as a way to simplify organizing their "life space" in view of smaller families and a longer period of employment in their adult future.

Pregnancy disability in normal uncomplicated pregnancy with vaginal delivery is estimated by the American College of Obstetricians and Gynecologists as 6 to 8 weeks in duration. Opinions of medical school chiefs of obstetrics in New York City (in an informal poll) differed as to appropriate length. Some would accept a period less than their ideal if that was the indicated way to get some leave period recognized in industry. Administratively, there is no particular difficulty in validating claims. The doctor certifying the claim would enter an expected date of delivery, and even if the actual date was not identical a payment period could be started from the first day of absence. If complications occurred, a medical or hospital document certifying that care had been received and that continuing absence was necessary would protect against use of the program for nonmedical reasons. A precoded list of medically recognized complications or concurrent illness could be established by a reputable medical body to assist a claims staff. The program could be used to assure a modicum of prenatal and postpartum care.

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* Title VII of the Civil Rights Act of 1964 forbids discrimination by employers, employment agencies, and unions on grounds of sex. Not only is this so for hiring, but also for compensation and terms of employment. The EEOC (Equal Employment Opportunity Commission) is the enforcing body. Its Sex Discrimination Guidelines (effective April, 1972) have a provision on "Employment Policies Relating to Pregnancy and Childbirth" which requires pregnancy-related disabilities to be treated like all other temporary disabilities. It applies to health and disability benefits, reinstatement and seniority accrual during leave. Termination of employment, if insufficient leave is available, is a violation. Maternity benefits must be available to women employees if available to wives.

For women already planning to stay at home, the disability benefit would serve as an income supplement. To many observers, this would seem like a reasonable price to pay for assuring an orderly protected absence in all pregnancies even if the mother had to or wished to return to work.

Conclusion

Financing emerges as a significant element in reproductive health policy once the capabilities of modern obstetrics and gynecology are recognized as too precious a social asset to allow distribution to depend on familial wealth and economic luck. Methods of financing a broad availability of women's health care and precedents for doing so are at hand and can be used, if the support for making requisite adaptations in these methods is found in society.

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Natural Law and Planned Parenthood

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The Conflict

Alan Guttmacher was first and foremost an obstetrician. But he was also one of the earliest and remained perhaps the most famous United States physician to speak out clearly for the need for abortion law reform. He wrote of his own evolving attitudes toward abortion and how it took him 47 years of careful thought to move from the goal of limited reform to the ideal of abortion on request (1). He hated the hypocrisy, cruelty and injustice of repressive abortion laws (2). He was proud to have been closely associated with the 1970 repeal of the New York abortion law and to have been a pacesetter in so many of the reforms and repeals which occurred from the middle 60's to the ruling of the United States Supreme Court in 1973.

Many people find a contradiction between dedicated care of the pregnant woman and the newborn child, and a forthright belief in abortion on request. For Alan Guttmacher there was no conflict. Why? The basic question is an old one. It is the most vivid of a series of problems involving medicine, biology, and morals.

Guttmacher's personal situation

The very nature of Guttmacher's life made the problem of fertility regulation particularly acute. He had a unique range of experience and responsibilities, which meant he could never escape the essential tensions of abortion and related problems. In addition to the satisfaction of exercising his professional obstetric skills, he gained immense personal pleasure attending childbirth. He estimated that he delivered 7000 babies and that he must have had the senior clinical responsibility for the delivery of "well over 100,000" (3). Yet each delivery remained an individually worthwhile event for him.

His numerical experience with abortion was less, but emotionally even more intense. Alan Guttmacher never suffered fools gladly. He knew how to be angry as well as immensely kind, and he detested the medical profession's treatment of women seeking abortion. He frequently talked and wrote of his early clinical experiences relating to an illegal abortion:

> When I was a second year student in pathology at Johns Hopkins University in 1927, I saw probably the most tragic autopsy of my life. A gaunt-looking woman, who was apparently entering the menopause, mistook two months' amenorrhea as evidence of pregnancy rather than evidence of the menopause; the poor soul had attempted to abort herself of a pregnancy that did not exist.

From the International Pregnancy Advisory Services, London and Chapel Hill.

> I can remember a Mrs. Knight, who had aborted herself, and gave me one of the most shocking experiences of my whole medical career. Most times death is kind. People lapse into coma, and they don't know the angel of death is waiting to take them off, but this woman, within five minutes of her death, pled for life in shrieking terms that time can never drown (3).

In Baltimore and New York, Guttmacher and his colleagues referred women to medically qualified illegal abortionists. He disliked the play-acting, but retained his curiousity about the practice of illegal abortion. One of his fellow students at Hopkins entered industrial medicine, but lost his job in 1929. "My friend was broke," describes Guttmacher (3), "when the daughter of the company's president conveniently became pregnant. The president paid him $5000 to abort her." Subsequently the man developed a thriving business and some years later returned to Hopkins trying to recruit an anesthetist. Guttmacher gave him lunch in the doctor's dining room and commented on the sleepless nights he had on the obstetric wards. "Why don't you do what I do? When I get tired I fly to Lima." Guttmacher recalls in his autobiography that he "naively asked, 'Lima, Ohio?' 'No, Peru,' " came the answer. How then did Alan Guttmacher reconcile the world of delivery of babies with his leadership in family planning and in abortion reform and repeal?

I think there were two essential elements in his life and beliefs which allowed him to develop a harmonious philosophy encompassing an unconcealed enthusiasm for obstetrics with an equally genuine compassion for abortion. One was a rejection of revealed religion and any belief in the supernatural, and the other a much deeper knowledge of the anatomy and physiology of mammalian reproduction than most physicians acquire.

Agnosticism is in no way a prerequisite for a realistic appreciation of the role of induced abortion in fertility control, but perhaps it enabled Guttmacher to see the issues clearly many decades in advance of his contemporaries. Guttmacher's paternal great grandfather had been Chief Rabbi of Grätz, near Posen, and a distinguished scholar. His father was for many years Rabbi of the reform synagogue in Baltimore. In 1915, when Alan Guttmacher was 16, his father suddenly died. He wrote in his *Memoirs:*

> It made me grow up in a few hours from a boy to a responsible young man. I had led a sheltered life carefully protected by caring parents. I had had no previous sobering experience, and in a flash my father, whom I adored, was no more. The second thing his death did was to divest me forever of a belief in God and organized religion. Suddenly, I realized I had been worshipping an anthropomorphic deity, my father, and with his death my God died too (3).

Guttmacher dated his own interest in embryology to childhood memories of watching sheep deliver in Druid Hill Park, Baltimore. It was an interest sharpened by being a uniovular twin. He was fascinated by his own embryologic origin, his left-handedness (and his teenage stutter when forced to write with his right hand), the fact that he talked late as a baby (because his nonverbal communication with his brother was so complete), and even by his terminal illness which followed tragically some years after his brother, Manfred, died from a similar blood dyscrasia.

Guttmacher entered John's Hopkins University in 1915 with the thought of reading English or history, but in 1918 he and his twin brother decided to enter the medical school. They rapidly became deeply immersed in pure science and Alan came close to becoming a professional anatomist. "The individual in the anatomy department," wrote Guttmacher in his *Memoirs*, "who made the deepest impression on me was Dr. George Corner." Corner developed Guttmacher's love of the history of medicine, as well as of embryology. In 1921 the twins, Alan and Manfred, tossed a coin to decide whose name should go first on their first scientific publication—Alan lost (4).

Nature's guidelines

The aim of the latter part of this paper is to categorize and review contemporary biologic observations that may assist in judging what is healthy and should be enhanced, and what may be unnatural, potentially dangerous, and should be avoided. The discussion goes beyond insights that help resolve the ethical issues posed by induced abortion. It asks how the statutes of natural law should be read in relation to human reproduction.

Spontaneous abortion. Mall completed one of the earliest studies of spontaneous abortion at Hopkins seven years before the young Guttmacher twins entered the University (5). He found that 37.5 percent of 435 abortions involved abnormal embryos. Rock and Hertig (who were busiest in the years 1938–1954, when Guttmacher was also at the height of his clinical career) carried the analysis of embryonic development back to the time immediately following fertilization. They estimated that 90 percent of fertilized eggs lived to the blastocyst stage, 50 percent to implantation, but only 42 percent survived until the 12th day of pregnancy (6, 7, 8). Thus more than half of all human conceptions may be lost even before the woman misses her first period, and becomes aware of the possibility of pregnancy may have occurred.

Chromosomal studies of material collected at spontaneous abortions confirm the situation. Carr found that 22 percent of 227 abortions had chromosomal abnormalities (9, 10). James had reviewed the whole topic of embryonic wastage and concluded that one fertilized ovum in three perishes before pregnancy is recognizable, and one in four or five is lost after the diagnosis of pregnancy is established (11). In total, he estimated one ovum in two is aborted spontaneously.

In biologic terms, spontaneous abortion appears to be a necessary natural healing process, in the absence of which the congenital abnormality rate at birth might be 1 in 5, instead of the current 1 in 50. And most abnormalities would be gross, not relatively mild as at present.

The criteria normally adopted in medical ethics are, "Is the procedure a healing one?" or "Does the operation add to quality of human life?". By these standards, induced abortion in cases of demonstrable fetal abnormality (that is, where the process of spontaneous abortion has for some reason failed) becomes mandatory. The door is also opened to abortion for social as well as physical pathology. Which is worse: to be a phocomeliac born to prosperous parents in Chicago, or an intact child born on the pavements of Calcutta?

In his *Memoirs* (3) Guttmacher describes what he called "one of the most dramatic operations I ever witnessed . . . still vivid through the haze of 54 years." It involved a woman brought from the mountains of Maryland to the Jewish hospital (later Sinai Hospital) in December, 1919. Fetal movements had stopped and at operation an extrauterine pregnancy was found. The surgeon "readily removed a normal appearing, large, dead baby boy," but in handling the placenta, which was attached to the intestines, he set off a hemorrhage from which the woman died.

In exceptionally rare cases, extrauterine pregnancies have not only gone to term, but have resulted in live-born children. At the turn of the century, Catholic theological opinion was that it was illicit to operate for ectopic pregnancy. Today the teaching permits surgery, justifying it by the pathology of the Fallopian tube, rather than by the deliberate intention to perform an abortion. Yet in truth this operation, in a statistically measurable number of cases, destroys a potential human life. Therefore Catholics, Protestants, Jews, Moslems, and atheists all stand on the same side of the line and agree that the mother's near certainty of health and life can take precedence over the more remote potential of health and happiness for the unborn child.

Abnormalities of the gametes. The hugely complex task of creating a mammalian embryo seems to have been partly achieved by an overproduction of conceptuses, combined with a system of biologic inspection. The same principle appears to apply to the formation of the gametes.

In mammals, the germ cells can be identified in the early embryo. In the human embryo they are microscopically visible within 20 to 30 days after conception. But by birth more than half the germ cells ever formed (5 million out of 7 million) have degenerated. It is not known how many of the ova that degenerate are abnormal, but it may be a large proportion. In women unlucky enough to have chromosomal abnormalities (such as Turner's syndrome), all the ova degenerate before birth and such women are permanently sterile.

A number of ova go on failing prior to puberty, and during fertile life only 300 400 will be used. Probably, some of the ova wasted during the fertile years are abnormal, although scientific techniques for their study are limited. The quality of ova appears to decrease with maternal age (12). More is known about abnormalities in sperm production, because they are accessible to study. Up to 1000 million are made daily. Why so many? Twenty to 40 percent of sperm from a healthy man are visibly abnormal and more sophisticated techniques of study demonstrate additional anomalies. The female reproductive tract is usually pictured as a place destined to afford the utmost protection to the delicate processes of development. In practice, it appears to consist of a series of formidable hurdles placed between the sperm and the egg. The anatomy of the cervix and the ostia of the Fallopian tubes are clearly not designed to assist the sperm locate the egg. There appear to be no chemotactic mechanisms directing the sperm to the egg, except perhaps in its immediate vicinity. During most of the menstrual cycle cervical mucus will not allow sperm to pass at all, and around the time of ovulation it still makes transit rather difficult. Of the hundreds of millions of sperm deposited in the vagina, only a few million enter the uterus, only thousands reach the Fallopian tubes, and possibly only a few hundred approach the ovum (13, 14). Probably nearly all defective sperm fail to make the course. Again, there are biological mechanisms for eliminating the abnormal.

The significance of fertilization. Reproduction is a long process which deserves to be reviewed, both biologically and ethically, in its entirety. It begins when the germ cells are set aside in the embryo and is still continuing when a grandmother babysits for her daughter's children. Fertilization establishes a genetically unique group of cells. However, it is not certain that it is the only way in which such a group can arise, and not all fertilized eggs give rise to embryos. Teratomas occur in both sexes and are not always related to the ovaries or testes. Hydatidiform moles develop without an embryo. They are the result of fertilization, they are genetically unique, but they have no more ethical status than the afterbirth.

Perhaps the significance of fertilization has been over-valued in sober theological argument as well as in the polemics that have accompanied the abortion discussion. In human terms, it is an event so remote that the woman has to wait at least two weeks to discover if it has taken place at all.

Rhythms and clycles. There appear to be a behavioral as well as anatomic and physiologic components to healthy reproduction. There is convincing evidence from animal experiments that fertilization with aged gametes raises the probability of fetal abnormality (15, 16, 17, 18). Epidemiologic studies linking human coital patterns and pregnancy outcome are difficult to conduct. So far they only involve small and nonrepresentive samples of the population. Jongbloef (19), for example, studied the offspring of a group of 35 families, each with one or more mentally retarded children. He found 33 abnormal pregnancies were accidentally conceived during the use of the rhythm method, but only 12 affected children in the group were conceived as planned pregnancies, when the parents were not following the rhythm method. Guerrero (20) found conceptions presumed to involve aged ova ended in spontaneous abortion twice as often as conceptions which followed insemination prior to ovulation (as measured by the temperature shift). The sex ratio also changes with the day of the fertilization (21), although it is not clear if this is due to differential loss of eggs, sperm, or fertilized ova. In a small series of cases, women who already had one or more abnormal children were advised to restrict intercourse to days 11 to 15 of the cycle; 15 out of 16 then produced healthy babies (22).

Ectopic pregnancy is a disease limited to man, apes, and old world monkeys. An association with menstruation seems possible. Iffy has suggested that conception, for whatever reason, late in the cycle may not be able to arrest endometrial disruption and the conceptus may be displaced to an abnormal extra- or intrauterine site. He showed that in tubal pregnancy, and in cases of placenta praevia, the embryo is often larger than the history of uterine bleeding would predict, which gives some support to the hypothesis (23, 24, 25).

There are also some reproductive cycles which have a life-long time base. The one certain thing that can be said about human reproduction in the contemporary developed world is that it follows a profoundly different pattern from that Homo sapiens was evolved to pursue.

For the vast majority of human history and pre-history, the menarche occurred in the middle or late teens, regular sexual intercourse probably began before or shortly after the first menstruation, and women then underwent a continuous series of pregnancies until the menopause. In the absence of contraception, pregnancy would occur after a few cycles and lactation probably continued for about two years, as in many traditional societies today. Menstruation was a relatively unusual process. In fact, it may be that this physiologically and emotionally wasteful process was only permitted to evolve because of its relative rarity. Frish has shown recently that the onset of the menarche depends on body weight (26, 27). Nutritional changes in the last century have brought down the age of menarche, in opposition to social changes which encourage later child bearing.

If contemporary epidemiologic patterns in developed countries were the sole criteria of normality, then lactation would have to be regarded as a pathologic secretion of increasing rarity. In reality, it is a prime variable in the natural regulation of fertility (28), and it is unfortunate that rich and poor in the exploding cities of the world are following the example of industrial nations. Repeated menstruation, instead of pregnancy and lactational amenorrhea, is becoming the rule throughout the world. In some way, certain changes in the life-long patterns of fertility noted above appear to have an adverse effect on health. Cancer of the female breast is many times more common in western than in traditional societies. Not all the factors leading to this change are understood, but there is a linear relationship between the age at which a woman delivers her first child and the probability of developing cancer of the breast– the younger, the less the risk (29, 30).

Some authors have suggested that exposure to many years of uninterrupted menstruation between the menarche and first delivery may be a relevant variable (31, 32). Japanese women have a lower incidence of breast cancer than women in the USA. But Japanese who migrate to USA suffer American levels of breast cancer after two generations (33). The age of menarche has fallen rapidly in Japan since World War II, as no doubt it did in migrants' children in the USA and their offsprings'. It will be important to see if the incidence of breast cancer rises in Japan.

Discussion

In several areas related to conception, abortion, and the life-long cycles of human reproduction, the facts of biology suggest that it is right and proper for physicians to offer certain therapies. They were all fields in which Alan Guttmacher himself was interested, and in several cases helped set national and inter national policies. But there are also areas where controversy exists. It does not need to be emphasized that many Catholic theologians read natural law in a very different way, and have outlawed abortion, adopted the rhythm method, and condemned the oral contraceptives. The Bible makes no mention of abortion. The Early Fathers of the Church had little embryologic knowledge, but at least some retained a reasoned perspective. "The law does not provide that the act [i.e., abortion] pertains to homicide," wrote St. James, "for there cannot yet said to be a live soul in a body that lacks sensation when it is not formed." It was only in the nineteenth century that near universal condemnation of induced abortion arose (34, 35).

Unfortunately, ethical judgments were made in advance of modern biologic knowledge. In several ways, induced abortion complements natural processes. But, just as nature endeavors, by screening out abnormal gametes and by the process of spontaneous abortion, to eliminate error early with a minimum of waste, so induced abortion must be performed early with a minimum of physical and emotional waste for the woman and maximum regard for the increasing complexity of the embryo.

Where does one draw the line: why not wait for the baby to be born and then kill it? The answer is not difficult, but it is arbitrary. It is this latter fact that has deceived many commentators. Guttmacher was a dedicated obstetrician and fought for abortion law repeal. Like other people, he found no difficulty distinguishing between an embryo and a newborn infant. It is a judgment with other, less emotional, parallels. Society must decide when an individual becomes legally adult. Should it be 16, 18, 21, or 30? That is a matter for discussion, but it is unanimously agreed that it should not be as early as six years or as late as 60. Similarly, few people are emotionally or legally disturbed by the use of IUD's, although they may act after fertilization, but infanticide is universally condemned. However, whether to limit induced abortion to 10 days, 12 weeks, or 28 weeks will continue to be a subject for debate.

The failure of Catholic theology to embrace oral contraceptives is equally tragic. Not only do pills mimic the natural suppression of ovulation occurring during pregnancy and lactation, giving virtually complete voluntary control of fertility, but it is an interesting biologic speculation to consider if they may not also restore the woman to a basically more healthy condition. Prospective and retrospective studies show a reduction in all forms of breast disease among oral contraceptive users, although the duration of use and numbers under consideration are insufficient at present to demonstrate if the effect extends to cancer (36). Even in advance of certain knowledge, one point of view needs to be established as a base for discussion; namely, the reproductive behavior of civilized women is not "natural." To do nothing and suffer decades of continuous menstruation is to take a decision, and it may not be the best one. Perhaps the use of steroidal contraceptives is less "unnatural."

Those interested in reproductive medicine need to develop the ethic of a lifelong concern for women, not only assisting in fertility regulation, but continually reviewing those factors that ensure women reach the menopause, and the decades beyond, in the healthiest possible state. Alan Guttmacher had such a perspective. His decision to accept the Presidency of Planned Parenthood was an important one for him and for the movement. It grew naturally out of his knowledge and concern for obstetric care. Good medicine reduces perinatal and infant loss. Therefore, to maintain the natural succession of parents by approximately two children who will survive to puberty, the individual and society seeks to regulate fertility. His decision to speak forcefully on abortion was a personal one born of conviction. It was structured and sustained by his deep understanding of embryology.

In the late 1960's he had thrust upon him a third decision: how should Planned Parenthood and the International Planned Parenthood Federation (of which he was the Chairman of the Central Medical Committee) respond to the adverse publicity concerning the pill? Had he condemned oral contraceptives because of their thrombotic effect, he could well have ended their use in the USA and many other countries. He knew the decision was a weighty one. He maintained the balance of evidence and favored continued use. In all three cases Guttmacher's decision had wide implications for millions of people; they were moral as well as technical decisions. I believe history will show Alan Guttmacher read nature's law more accurately than most of his contemporaries.

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Dr. Alan F. Guttmacher: As Remembered by a Latin American Physician

BENJAMIN VIEL, M.D., M.P.H.

To be remembered with affection by a circle wider than one's relatives and intimate friends is what distinguishes men of superior quality from the rest. Whoever has dealings with medical people in Latin American countries is sharply aware that the memory of Alan Guttmacher remains alive among them. Without any question, this is also true in circles in Europe, Africa, and the Orient.

Dr. Guttmacher was not the discoverer of new methods of treatment; he did not isolate a new antibiotic nor did he find a chemical formula that would provide rapid treatment for any of the numerous human ailments. He was, however, an outstanding doctor in his specialty, obstetrics and gynecology. He won, and deserved to win, the gratitude and affection of those who were his patients. But is that enough to be remembered in the way he is remembered? Or did he possess other qualities beyond those which mark the great specialist?

He decided to enter obstetrics and gynecology when he was still a young doctor. Within his specialty, he learned what was known in his era, gained a wide range of experience and contributed greatly to the enormous progress made in recent years. He became an excellent example of a doctor who seeks to bring relief to those who suffer. But that was not enough for a man who realized he had something else to offer. His generous spirit led him into teaching.

To talk with those who were his students is to become convinced that Alan Guttmacher was something much more than a professor offering instruction in techniques. He molded other doctors who would be capable of continuing his noble goals when the time came for him to put down his burden. He was a shaper of minds who knew how to inculcate in his students the notion that a doctor is meant to treat not just a portion of the human body but to treat the entire, indivisible human being who is suffering and who has asked for help.

His status as a specialist and as a professor in the specialty would have been quite enough to satisfy the ambition of most men, but it was not enough for Alan Guttmacher. He provided his skill to the woman who asked his help in childbirth. He offered not only his skill but also his affection to those who sought relief from gynecologic illness. He was educated in the precepts of his era, and he heard from his own teachers that the duty of the obstetrician is to help the woman through the process of reproduction while that of the gynecologist is to repair those infirmities or defects that might interfere with this process.

But he went further than this. Because he treated the patient as a whole he was often told in confidence of her anxieties, and in this way, he learned that there were many women who did not want to be pregnant. Out of his feelings for humanity he turned to the problem of the unwanted child.

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His encounters with the unhappiness and the anxieties of humanity led him into the ranks of those who pioneered for the human right to decide on the time of parenthood when that concept was still considered immoral.

In this way, Alan Guttmacher broke down the boundaries of his specialty. He showed that the obstetrician-gynecologist has much to teach the pediatrician. He also had much to teach to those, such as myself, who were working in public health in Latin America. It was thus that I first met him; it was from him that I learned that to prolong the lives of many people it would be necessary to prevent a large number of births, and that this could be achieved by helping the woman to exercise her right to transform instinctive motherhood into conscious motherhood. I learned from him that the privilege of physical and mental health is possessed only by those who had the benefit of having been wanted as children.

Convinced that he had a message to put forth and that it would not be enough to teach only within the boundaries of his own country, Professor Guttmacher converted himself into the eternal traveler. There was no time for weariness, nor was he detained even when he found out he was ill. His message, expressed in the habitual elegance of his language, was heard on all continents. Today, the tireless fighter has found rest at last, but his words remain alive among the doctors and nurses who serve the clinics of the United States, Asia, Africa and Latin America. His message also remains alive among teachers who instruct children in the biology of reproduction and in the sense of responsibility that sexual conduct involves.

Surrounding his memory is the gratitude of all the women who received his care and of all those who continue to receive advice and services in the well-equipped clinics of the developed world. To this must be added the gratitude of all those anonymous women who probably never so much as heard the name of their benefactor but who today can be found in attendance at the humble clinics in mountainous Andean villages, on the tragic floodplain of Bangladesh, and in the jungle regions of central Africa.

Not only a good doctor and a great teacher, Alan Guttmacher was also a humanitarian who fought within and outside his country for the rights of the individual and the welfare of humanity. His name has become part of history in that niche appropriate to people who have conspired against the pain and misery of the world.

Experience with Intrauterine Contraception by Adolescent Women*

MARY E. LANE, M.D. AND AQUILES J. SOBRERO, M.D.

Alan Guttmacher was closely associated for more than twenty years with the Margaret Sanger Research Bureau, which for fifty years pioneered in service, research, and training in the control of human reproduction. He was the Bureau's director from 1959 to 1962. As a proponent of thoughtful sexual and contraceptive education for maturing individuals, he was an ardent supporter of the Bureau's Teen Center which from February 1971 through May 1973 provided such care primarily to self-referred young women, aged 17 and under, and their sexual partners.

The Teen Center's experience with the provision of intrauterine contraceptive devices (IUD) to its young clients is of interest in view of the continued resistance among family planning workers to the use of IUD by adolescent women. That this reluctance is related in part to the issue of nulliparity is illustrated by a study reported by Marinoff and Fiedler (1). These authors showed that in two clinics serving women under the age of 17, each woman in the first clinic having borne a child and the large majority in the second never having been pregnant, there was a high ratio of IUD to oral contraceptives prescribed in the first and a complete reversal of this ratio in the second. There is, however, ample evidence that neither nulliparity nor nulligravidity is a contraindication to intrauterine contraception (2–8). The authors therefore, will address the issue of age *per se*.

Notwithstanding current discussion about the safety of IUD, there is no disputing the fact that pregnancy poses a greater risk; it is also unlikely that potential complications of intrauterine contraception outweigh those of hormonal contraception. An Ad Hoc Advisory Committee to the Food and Drug Administration on Obstetrics and Gynecology has stressed that "IUD's as a class are considered to be a relatively safe and reliable means of contraception, comparing favorably with oral contraceptives" (9). Therefore so long as epidemiologic data do not support the discontinuance of intrauterine contraception, there will be a proportion of women, adolescents among them, who for personal reasons will prefer to use this method over all others. This report describes the experience of the Margaret Sanger Research Bureau with the provision of IUD to clients of its Teen Center—an experience which the authors believe justifies a more positive attitude toward the use of IUD by women of this age group.

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Material and Methods

Between 1 March 1971 and 31 December 1972, 399 women were enrolled in the Teen Center, and at some time during the 22-month period 101 of them (25%) selected the IUD as their contraceptive method as against 50% choosing hormonal contraception; 15%, diaphragm and jelly; and 10%, foam and condom (which was for the most part a temporary method). This is compared with the 28% of women of all ages, the clientele of the Contraception Service at large, who in 1971 selected the IUD, and the 40% who did so in 1972, when the copper-bearing devices were made available to them. Table I shows that the teenage selectors ranged in age from 13 through 19 years (median age 16 years) and that 83% were nulligravid, 96% were nulliparous. The five women aged 18 and 19 were exceptions to the Teen Center age limitation and were cared for in this special service because of their apparent emotional immaturity. While in most cases, the staff considered parental knowledge to be an asset in the care of these young people, we felt that our primary responsibility was the protection of our clients, as promptly and effectively as possible, from unwanted pregnancy; therefore, parental consent was not treated as a prerequisite to the provision of contraceptive care in general or to the prescription of any method in particular.

In the Teen Center, method choices were usually made in the company of other adolescents (new and revisit patients) and frequently of their boyfriends, in an unhurried and nonharassing clinic atmosphere. All shared in a discussion with one or more members of the staff (social worker, nurse, physician, or volunteers from among the clientele), in the course of which all the medically accepted methods were thoroughly described in a manner which sought the utmost objectivity. It was hoped that the support and assistance of peers at this time would encourage each new client to exercise personal preference for a method in accordance with personality and with current sexual and social needs. This group session was also the vehicle for describing the pelvic examination, diaphragm fitting, and the IUD insertion procedure. Individual advice was

TABLE I

Demographic characteristics of 101 Adolescent IUD acceptors

	Number	Percent
Age		
13–14	6	5.9
15	21	20.7
16	39	38.6
17	30	29.7
18–19	5	5.0
Gravidity		
0	84	83.2
1	17	16.8
Parity		
0	97	96.0
1	4	4.0

TABLE II

Devices used in 130 IUD insertions in 101 Adolescent Women

Device	First Insertion		Reinsertion		
	Number	Percent	Number	Percent	Following:
W	2	1.9	2	6.9	LEM expulsion
LEM	54	53.4	1	3.5	LEM expulsion
Loop C	44	43.5	13	44.8	LEM expulsion (7) LEM removal (2) Loop C expulsion (2) Loop C removal (2)
Loop D	1	1.0	13	44.8	LEM pregnancy (3) Loop C expulsion (8) Loop D expulsion (2)
Total	101	100.0	29	100.0	

given in as unbiased a manner as possible, and unless the method chosen by the patient was contraindicated for medical reasons, it was usually prescribed. Exceptions to this rule were those few cases wherein a request for IUD was associated with a high level of anxiety such that the woman's ability to tolerate an insertion on that occasion was deemed unlikely; in such cases, the procedure was deferred or the young woman was encouraged to select a different method.

Among the 101 selectors, the IUD was the first contraceptive method for 11; for the other 90 it followed the use of one or more different methods. During the 22-month study period, 22 young women underwent insertion a second time after expulsion or removal of a device, and seven of these a third time, for a total of 130 IUD insertions.

The devices used were of four types: Loop C, Loop D, LEM (10), and W (Table II).* The LEM was a very pliable four-legged radiopaque polyethylene device with a monofilament nylon thread as transcervical appendage. The W was a strand of stainless steel wire in the shape of the letter W, totally enclosed in a polyethylene-polyurethane membrane; it had two transcervical appendages of dacron. Lippes Loop C differed from the Loop D not in size but in its slightly greater flexibility, and in our contraception service was customarily used for the nulligravid or nulliparous woman, being replaced usually by Loop D if expelled. These conventional plastic devices (Loops C and D) constituted 55 percent of the 130 devices used in our Teen Center during the period under study. They were employed for most of the reinsertions, the LEM and W being rarely used for this purpose. The small Loop B had not been used in our clinic for many years, and the even smaller size Loop A not at all, because of an unacceptable risk of expulsion and pregnancy associated with them (2).

Eighty-five percent of the insertions in the present study were performed by two attending physicians, the other 15 percent by medical fellows and one family planning nurse practitioner. Insertion was made approximately one-half hour following administration of two tablets of a mild analgesic* and after breast and pelvic examination (including culture for gonorrhea and Papanicolaou smear) and thorough sponging of the portio vaginalis and cervical canal with antiseptic solution. A tenaculum was used consistently to steady the cervix and straighten the uterine flexure somewhat. The LEM and the W were inserted by means of the withdrawal technique, through which the device is released at the fundus by retracting the insertion tube over it; in general, this is a less painful and hazardous method of insertion than is the pushing technique used for the Loop. All mechanical procedures were performed with extreme gentleness and patience and in a deliberately unhurried manner.

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* Lippes Loops C and D supplied by Ortho Pharmaceutical Corporation, Raritan, N. J.; LEM supplied by Marco and Son, Inc., Old Bridge, N. J.; and W supplied by Frank Shubeck, M.D.

No additional method of contraception was advised for IUD acceptors, but they were advised to search for the cervical appendage at least after each menses. They were examined again four weeks following insertion and at least every three months thereafter, in conformity with the revisit schedule of all the Teen Center enrollees, whatever their method of contraception. In addition, they were asked to return in the event of occurrence of undue pain, excessive bleeding or discharge, any indication of expulsion, delayed menses, or any dissatisfaction with the method—in which latter case a change of method was encouraged. A patient who did not respond in any way to follow-up attempts by six months after a scheduled visit was considered lost to follow-up; seven women fitted this description. One woman was released to another source of care.

Results

It is not the intent of this report to analyze the performance of the devices by type, even if their numbers had been large enough to support this. While a few clinical observations will be made pertaining to the type of device, our basic purpose is to focus on the overall continuation of the study group having among them a significant proportion of reinsertions. Therefore, the method of data analysis described by Tietze (11) is used, which allows for the inclusion of data on second and later segments of use (i.e., periods of use following reinsertion). In this study the longest period of analysis possible by this method is nine months, since at that point the woman-months of use during one ordinal month drops below 50. Results are shown in Table III, where distinction is made between net cumulative event and closure rates per 100 women.

Removal of a device because of bleeding and pain occurred in 15 instances during the 22 months (once for every nine insertions). Thirteen of these removals occurred by the end of the ninth ordinal month, for an event rate of 13.6 per 100 women. However, three of the 13 women underwent reinsertion, so the closure rate for bleeding and pain was only 10.4. While insertion was easily performed in most instances, it was associated with severe pain in 18 instances (one in seven) either during the procedure itself, immediately thereafter, or during the first 24 hours (Table IV). Two of these patients vomited, and two others fainted. Eighty percent (14) of these painful episodes were related to Loop insertions. Nine devices were removed within 24 hours because of pain—seven of them within the first one or two hours. Eight of these nine were Loops. There was a somewhat greater frequency of early removals among the nulligravidae one early removal in 13 insertions—as against one in 23 insertions in gravid women, in concurrence with Tietze's observations (3).

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* Tranco-gesic (Winthrop Laboratories), containing aspirin 300 mg, chlormezanone 100 mg.

Six devices associated with minimal or only moderate pain on insertion were removed later for pelvic cramps, dysmenorrhea, and excessive bleeding, all within the first five months after insertion; four of the six were Loops.

On the other hand, Table IV shows also that 63 percent of all insertions were

TABLE III

Net cumulative rates of events, closures, and continuation per 100 IUD acceptors

Period of Observation (months)	Type of Event or Closure						Total Closures	Continuation	Woman-Months of Use
	Accidental Pregnancy	Expulsion		Removal					
		First	Later	Bleeding and Pain	Other Medical	Personal			
1									
Events	0.0	8.2	0.0	8.2	0.0	0.0			
Closures	0.0	2.0	0.0	6.1	0.0	0.0	8.1	91.9	94
3									
Events	1.1	13.4	0.0	11.3	2.1	1.2			
Closures	0.0	2.0	0.0	9.3	2.1	0.0	13.4	86.6	262
6									
Events	1.1	16.8	2.5	13.6	5.4	2.2			
Closures	0.0	4.3	0.0	10.4	5.4	1.2	21.3	78.7	480
9									
Events	3.8	20.9	3.9	13.6	5.4	2.2			
Closures	1.4	7.0	1.4	10.4	5.4	1.2	26.8	73.2	650

TABLE IV

Outcome of 130 IUD insertions in 101 adolescent acceptors, by amount of insertion discomfort

Amount of Discomfort	Insertions		Removal for Pain and/or Bleeding	Subsequent Closure for Any Other Reason	Continuing Users
	Number	Percent			
Severe on insertion, immediately afterward, or during first 24 hr.	18	14.0	9	6*	3**
Moderate during or immediately after insertion	30	23.0	4	9	17
Minimal to none	82	63.0	2	39	41
Total	130	100.0	15	54	61

* Includes 2 with syncope.

** Includes 2 with vomiting.

accompanied by minimal or no pain; that pain was sufficient reason for removal in only nine of the 18 women who were intensely uncomfortable during or after insertion; and that three of this group of 18 remained active throughout the observation period.

There were 25 first expulsions and six later expulsions (following one or more reinsertions) during the 22 months; i.e., one out of four devices was expelled. Nineteen of these expulsions occurred by the end of the ninth ordinal month, for an event rate of 24.8 per 100 women. However, since 12 of these women underwent reinsertion, the closure rate was only 8.4. Thus, while expulsions outnumbered removals for bleeding and pain, closures after expulsion were second in frequency to closures for bleeding and pain. Though roughly 25 percent of both Loops and of LEM were expelled, all Loop expulsions occurred within seven months of insertion—55 percent during the first month -while almost 40 percent of the LEM expulsions occurred as late as 9 to 14 months after insertion.

Four of the five removals for medical reasons other than bleeding and pain were for pelvic inflammatory disease, the fifth for psychosomatic symptoms. None of these was followed by reinsertion.

Five accidental pregnancies occurred during the 22 months of observation, three within the nine-month period of analysis, for an event rate of 3.8 and a closure rate of 1.4, since two of these three patients underwent reinsertion following abortion, the option chosen by four of the five pregnant women. The device used was the LEM in each case, and in two of these instances a partial expulsion was discovered at the time the pregnancy was diagnosed. The other two pregnancies also occurred in association with the LEM, 14 and 19 months after insertion. The LEM pregnancies and the tendency of this device toward expulsion late in the course of use stemmed very likely from its extreme pliability—that property responsible for its relative comfort but which allowed it to descend over a period of time into the lower uterine segment in response to uterine contractions. We began to remove the LEM electively when the pattern of pregnancies became apparent; however, since these removals for "investigator's choice" did not commence until April 1973, they are not reflected in this analysis.

Only two women discontinued for personal reasons during the entire 22-month study period, and one of these underwent reinsertion. The total closure rate at nine months was 26.8 per 100 women; the continuation rate was 73.2.

Of the 32 women ultimately discontinuing intrauterine contraception, 14 chose hormonal contraception, 13 diaphragm and jelly, and one rhythm. Two had made no contraceptive decision at the time of the analysis. The remaining two abandoned contraception, voicing the intention to cease exposing themselves to risk of pregnancy. Of the 61 continuing users beyond the end of the 22-month observation period, 34 were wearing Loops—nine of them Loop D.

Comment

The low closure rates in this study in comparison to the event rates cannot be ignored. The fact that out of 101 clients 22 freely chose to try another IUD after an unsatisfactory experience with the first one and that seven of these actually tried a third time despite the free availability of other effective contraceptive methods is indicative of a level of motivation and a resolve to make the method work not universally ascribed to teenagers. Of the 61 active users at the end of the observation period, ten had had reinsertion one after removal for pain, one after accidental pregnancy, four after one previous expulsion, and four after two expulsions.

A number of reports show lower rates of continuation among users of oral contraceptives than among IUD users, even when age and other sociologic variables are controlled (12). These suggest the importance of patient motivation in choice of method and in its length of use. The nature of our young clients' motivation is revealed by the reasons they stated for choosing IUD; in order of frequency, these were: failure to adjust to previous methods tried; side effects with previous methods; quest for convenience; quest for contraceptive security; need for continuous protection; anticipation of side effects or of ineffectiveness of other methods; a change in frequency of coitus (in either direction); and a desire for secrecy in the use of a contraceptive method.

The question of superiority of one device over another is not of importance to this discussion, as all presently available devices have their advantages and their drawbacks. It is clear that the most comfortable device will not prevent pregnancy if it is expelled; the best retained device will not be accepted by the patient for very long if it is painful; nor is long-term satisfaction likely to be associated with a method which has been urged upon the user. But given a high level of motivation on the client's part and a truly informed choice, and given staff support of the nature described in this report, the authors feel that the IUD is a viable contraceptive option for the adolescent woman.

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Ernst Gräfenberg and His Ring

HANS LEHFELDT, M.D.

When Alan Guttmacher was born in Baltimore, Maryland in 1898, Ernst Gräfenberg was a teenage boy of 17 living in Germany. Later, circumstances brought the two men into closer proximity. From 1940 to 1957, both lived in the United States, and for five years in the same city, New York. Both men were associated with the Department of Obstetrics and Gynecology at The Mount Sinai Hospital in New York: Guttmacher as its chief from 1952 to 1962 and Gräfenberg as an assistant in the Outpatient Clinic in the 1940's. In spite of many opportunities for their paths to cross, the two men never met—a pity, as they had much in common. They shared the rare combination of being outstanding gynecologists and scientists and being endowed with charisma; pioneered in the birth control movement and in the struggle for acceptance of contraception as an integral part of medical practice; and fought for liberalization of the abortion laws, motivated by a deep compassion for the problems of the poor.

Ernst Gräfenberg was born on September 26, 1881, in Adelebsen, Germany. The little town was surrounded by hills, one of them named Gräfen-Berg (Counts' Hill). In the 19th century, when Jews were allowed to acquire family names, Gräfenberg's family took the name of this hill.

Gräfenberg attended elementary school in Adelebsen and high school in Göttingen, graduating in 1900. He studied medicine at the Universities of Göttingen and Munich, and passed the Medical State Board examination in Göttingen in January 1905. His doctoral thesis, "Die Entwicklung der Knochen, Muskeln und Nerven der Hand," (The Development of Bones, Muscles and Nerves of the Hand) was selected for the Petsche Prize of Göttingen University and published as a monograph by the prestigious publisher, J. F. Bergmann. After obtaining his doctorate summa cum laude, Gräfenberg became assistant in the Department of Ophthalmology at the University of Würzburg, where he published two papers on eye diseases. He then decided to study gynecology and was accepted at the Department of Obstetrics and Gynecology of the University of Kiel—a not inconsiderable feat for a young Jewish doctor in the Germany of the early twentieth century. He became assistant to Richard Werth and later to J. Pfannenstiel, two outstanding gynecologists of that time. In 1910 he started a gynecologic practice in the Berlin suburb of Schöneberg.

Gräfenberg was at the height of his career in Berlin in 1928. He had an office on the fashionable Kurfürstendamm and included among his patients celebrities from the stage and opera, and the wives of wealthy businessmen and diplomats. He was also head of the gynecologic department of a municipal hospital. I asked to be his assistant. He did not need an assistant, but invited me instead to accompany him on his hospital rounds. Located in Britz, a district of Berlin mainly inhabited by a workingclass population, the hospital contained many rows of beds with women who had undergone or were scheduled for abortion. Gräfen-

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berg saw to it that these low-income patients benefited from the same liberal indications for abortion that were generally reserved for the wealthy.

I also was greatly impressed by his surgical skill. A student of Pfannenstiel, Gräfenberg frequently used the transverse incision named after his teacher.

In 1934, I tried to persuade Gräfenberg to leave Germany. He decided to stay, feeling perfectly safe with wives of high Nazi officials as his patients. He was wrong. Denounced for having smuggled a valuable stamp out of Germany, he was sent to a jail near Berlin in 1937. He seems to have been well treated there, possibly because the prison warden's wife was a patient of his. When Margaret Sanger heard about Gräfenberg's imprisonment through the American consulate, she negotiated his release by paying a large ransom. Gräfenberg finally left Germany in 1940.

Because of the war, he had to travel via Siberia and Japan and debarked in California. In Hollywood, he found old patients and friends. Erich Maria Remarque loaned him the money to start a new existence in the United States. He first worked in Chicago as a pathologist and prepared for his Medical Board examination which he passed in 1941. Several colleagues had warned him against New York City as too competitive, but I suggested that there was no better place for him to practice than New York, where so many of his former patients were living, and indeed, he soon developed a large private practice.

In his later years he suffered from progressive Parkinson's disease and was forced to reduce his activities. In 1947, he retired from The Mount Sinai Hospital; in 1950, from Sydenham Hospital; and in 1953, after an attack of ileus, gave up his practice and his work at the Margaret Sanger Research Bureau. He died on October 28, 1957. There was no obituary and no announcement of his death in the *New York Times* or in any medical journal. Only the German-language weekly *Aufbau* published an obituary paying tribute to a great physician and scientist.

While compiling Gräfenberg's bibliography, I became aware of the wide range of his scientific interests. While still a student, he published a paper in the *Anatomische Hefte* on an embryologic subject dealing with the development of the pelvic muscles in the human. His early articles from the University of Kiel are case reports. Later he published papers on dysmenorrhea and tuberculosis, anesthesia problems, and the use in obstetrics and gynecology of Pantopon,® an opiate then newly discovered by Sahli. In the years 1909–1911, he wrote on the interrelationship between congenital syphilis and congenital malformations and published a study on the prognostic value of the blood count in puerperal diseases.

Gräfenberg started his research in reproductive physiology in Berlin. His animal and laboratory investigations focused on the antitrypsin content of the maternal serum during pregnancy and on the physiology of nidation. At about the same period he also began to study the sex-specific toxicity of testicular antiserum, as well as anaphylactic relations between mother and child during pregnancy. These studies originated from the Pharmacological Institute of Berlin University and were carried out in cooperation with an associate at the Institute,

J. Thies. This work is noted in Bumm's *Textbook of Obstetrics* and in the Halban-Seitz *Handbook*.

His last article before the outbreak of World War I dealt with the specific influence of x-rays on fibromyomatous tissue. Being an officer in the German army did not stop the flow of his publications. During World War I six papers appeared dealing mainly with the treatment of thoracic and abdominal gunshot wounds, and an amusing piece was published in the *Deutsche Medizinische Wochenschrift* describing the makeshift obstetrical forceps improvised by him while on the Eastern front, which he used for delivering Russian peasant women in their homes.

The war had interrupted Gräfenberg's work at the Pharmacological Institute. One of his more important projects concerning the cyclic changes of the acidity titer of the vagina, was finally published in 1922 in the *Archiv für Gynäkologie*. This paper was widely discussed in scientific circles and was incorporated in R. Th. Jaschke's chapter on vaginal physiopathology in the Halban-Seitz *Handbook*. Gräfenberg's clinical investigations indicated that human vaginal acidity is subject to cyclic changes and is lowest at ovulation time, thus intensifying the chances of fertilization. Continuing his investigations in this field, he found that roentgen rays influence the acidity of the vaginal secretion. These findings were presented at the German Gynecological Congress in Innsbruck, 1922, and again published by Jaschke in the Halban-Seitz *Handbook*. Gräfenberg received credit for being first in establishing that these cyclic changes in vaginal acidity are physiologic.

In the middle 1920's, Gräfenberg became interested in serologic diagnostic problems. One of his papers concerned the diagnosis of gonorrhea by means of the complement fixation technique. In cooperation with H. Munter, he also developed a serologic test for the diagnosis of early pregnancy, using formalin-placental antigen extracts. Gräfenberg published another paper on placental antigens in 1929.

Gräfenberg was also interested in sexology. In 1928, he was a member of the Board of Directors of the International Association for Sexual Science. In a paper on his intrauterine method of contraception presented in 1929 at the International Sexual Reform Congress in London, organized by the World League of Sexual Reform under the presidency of Magnus Hirschfeld, Gräfenberg stated that "a satisfactory contraceptive method is most important in dealing with psychosexual disturbances in women. By removing fear and the necessity for objectionable preparations, many physical and mental inhibitions are removed." Similar thoughts are expressed in Gräfenberg's article on the cervical cap written in the United States together with Robert L. Dickinson in 1944. In this country he became acquainted with Kinsey and the Institute for Sex Research, and his own sex history is among those published in the famous Kinsey Report. During the last years of his life he published a number of articles in the field of sexuality, which are quoted in the second Kinsey Report and in the two first books by Masters and Johnson.

Gräfenberg was deeply involved in the birth control movement from its earliest stages. He met Margaret Sanger and Robert L. Dickinson while practicing in Berlin in the 1920's, and they became close friends for the rest of Gräfenberg's life.

Gräfenberg started his investigation on intrauterine devices (IUD) in 1920 in Berlin. He first presented his method at a postgraduate course organized by Margaret Sanger in Berlin, in December 1928. In September 1929, at the Sexual Reform Congress in London, and again in September 1930 in Zürich, at the Seventh International Birth Control Conference, Gräfenberg lectured on intrauterine contraception. His fourth and last presentation on IUD's was given in 1931 in Frankfurt, at the Conference of German Gynecologists. In contrast to his previous communications, this one was very short, consisting of only 17 printed lines; it unleashed a tempest of controversy. Most of the leading gynecologists, among them L. Fraenkel (1) and S. Aschheim (2), denounced the Gräfenberg ring as extremely dangerous, with the result that from then on very few physicians continued to use intrauterine contraception.

In the spring of 1962, a conference on IUD's was held in New York City, sponsored by the Population Council (3). Alan Guttmacher served as chairman of the Conference and as a member of the steering committee. In his opening remarks he stated that intrauterine contraception had fallen into disrepute. "Even if the newest modifications of the Gräfenberg ring prove to be safe and efficient, it is going to be extremely difficult to rehabilitate this method. . . . If it is efficient and safe, we must do everything we can to push it," Guttmacher said. This first IUD Conference started the renaissance of intrauterine contraception. Tribute was paid to the "genius of Gräfenberg" (Herbert Hall), regret was expressed that he had not lived to see the "acknowledgment of his great idea" (Jack Lippes), and the history of the IUD was thoroughly and authoritatively described and documented (4, 5).

While Gräfenberg was not the first nor the only gynecologist to use the IUD, he was first to investigate the device on a scientific basis, by clinical observation with follow-up and comparative studies of various IUDs. In addition, he did endometrial biopsy studies in IUD wearers together with Robert Meyer, an outstanding German gynecologic pathologist. His studies and observations led Gräfenberg to the conclusion that all tailed IUDs had the same disadvantage, namely that appendages established a communication between the sterile endometrium and the nonsterile vagina.

The fact that all modern IUD's have appendages, usually of nylon, in spite of Gräfenberg's warnings against them, is due to the research done by J. Lippes together with E. Witebsky (6, 7), which showed that no bacterial invasion of the uterine cavity is caused by the thread attached to the IUD. A possible exception to this rule was noted very recently by H. Tatum (8) who, while affirming that the most commonly used nylon tails for IUD's do not cause uterine infection, pointed out that the particular multifilament tail of one IUD, the Dalkon shield, may act as a "wick" in spreading infection from vagina to uterus.

The original Gräfenberg IUD was made of silkworm gut, first in the shape of a star and then of a ring. The ring shape had lower expulsion and pregnancy rates.

Later, Gräfenberg replaced the silkworm gut entirely by silver wire, after having observed that this material produced the lowest pregnancy rate as well as the lowest incidence of inflammatory reaction. As we know today from Tatum's (9) investigation, the German "silver" used for the Gräfenberg ring contained 26% copper, and the studies of Zipper et al (10) have shown the high contraceptive effectiveness of copper. According to Fiscina et al (11), copper also seems to have anti-infectious qualities. These findings confirm Gräfenberg's early observations.

Examination of the endometrial biopsies done by Gräfenberg and Meyer showed the absence of any inflammatory reaction in the endometria of IUD wearers. These findings convinced Gräfenberg that the contraceptive effectiveness of the ring was due neither to inflammatory reaction nor to "purely . . . mechanical irritation" of the endometrium, and he concluded that the ring derived its contraceptive effect by preventing nidation of the fertilized ovum. His observation of several ectopic pregnancies with the ring in situ seemed to support this hypothesis. Today, more than 40 years later and in spite of extensive research in this field, we still have not succeeded in establishing the modus operandi of the IUD.

In his papers, Gräfenberg discussed at some length the technique and timing of insertion and removal of IUD's. Many of his suggestions are being rediscovered today by physicians unaware of Gräfenberg's original work. He recommended working under strict aseptic conditions. He designed a tenaculum, specially manufactured for him by Krupp, to reduce the risk of perforation and to minimize traumatization of the cervix by straightening out the uterus. The two prongs of this stainless steel instrument are exactly opposite each other, thereby also minimizing pain at application. To avoid inadvertent insertion into a pregnant uterus, Gräfenberg recommended the menstrual period or the time immediately thereafter as the optimal time for insertion. He suggested postponement of insertion until six weeks postpartum. All of these recommendations are today considered sound medical practice. As to the ideal time for removal of the IUD, Gräfenberg wrote: "If the IUD is removed during the intermenstrual period, it has been observed in some cases that menstruation fails to take place—and the woman becomes pregnant. My explanation for this phenomenon is based on the hypothesis that at the time when the ring was removed there was a fertilized ovum migrating, but not yet in the uterus. It is safest to remove the ring only when the first signs of menstruation are noticeable" (12). The same suggestion was made in an article in *Lancet* in 1971 (13) without an attribution to Gräfenberg.

Other suggestions relating to utilization of the ring show Gräfenberg's scientific thoroughness and his feeling of responsibility for his patients. Even though he and others had observed pregnancies with the ring in situ carried to term and resulting in healthy babies, he recommended interruption of accidental pregnancies with IUD in situ. He also advised replacement of the silver ring every year. The plastic, inert IUD's in use today make this precaution unnecessary. Recommendations for copper-bearing devices, however, also include early removal in case of accidental pregnancy with the device in situ, and replacement of the device after 2 to 4 years.

Gräfenberg intended to write a history of his ring. I had assembled for him all the relevant old documents and materials, which he had lost in the course of his various migrations, from my own library. Unfortunately, his deteriorating physical condition made it impossible for him to realize this project. It was while preparing this paper that I learned that Gräfenberg continued his work on intrauterine contraception during his years in the United States. The development of the stainless steel ring was done under his aegis, in cooperation with Herbert Hall. He himself used this modified version of his ring in his New York practice. But, following the advice of Dickinson, he kept this fact secret, not even mentioning it during a meeting at my house with Norman Haire, in December 1951. Still, the fact is irrefutable.

We have come a long way from the early days of pioneering for birth control and for liberalized abortion. Guttmacher, fortunately, lived to see the fruits of his life-long efforts; Gräfenberg was deprived of the reward of seeing his work accepted and his ideas realized. Both left us too early. Yet, their contributions and untiring devotion are firmly established in the history of population control.

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The Loop Decade*

JACK LIPPES, M.D. AND MARIA ZIELEZNY, PH.D.

A Referral

In August 1959, an article on the Gräfenberg Ring by Oppenheimer in the *American Journal of Obstetrics and Gynecology* inspired me to begin to investigate IUD's as a promising method of birth control. My first step was to ask Alan Guttmacher whether he believed that the abandoned concept of intrauterine contraception should be reassessed. Dr. Guttmacher replied that he had no opinion about the advantages or the disadvantages of IUD's, but he referred me to Dr. Christopher Tietze, who did have an opinion. Dr. Tietze's opinion that IUD's should be reevaluated was certainly known to Alan Guttmacher. Dr. Guttmacher understood that this referral might result in additional studies to reevaluate intrauterine contraception. My first experiments with IUD's began. It was to culminate in the development of the loop.

The loop was introduced at the First International Conference on Intrauterine Devices, which Dr. Guttmacher helped to organize in 1962.

J.L.

Interpretation and statistical analysis of the data concerning utilization of the loop over a decade is presented in this paper. Handmade loops the size of Loop A were made in 1961; by late 1961 or early 1962, Loop A was injection-molded (1). It had a cross-sectional diameter of 2 mm by 1.4 mm while the top bar measured 25 mm across. After one year (i.e., 1962 to 1963) a 5% pregnancy rate and a 22% expulsion rate was observed for Loop A. Both rates were deemed too high, and subsequently Loop A was abandoned for the multiparous patient. Loops C and D with cross-sectional diameters of 2 × 2.8 mm and top bars measuring 30 mm in length were designed in 1962. Because of larger overall dimensions, these devices had lower pregnancy rates. By increasing the cross-sectional diameters of Loops C and D and thereby decreasing flexibility, the expulsion rates were decreased (2).

Materials and Methods

To assess 10 years' experience with the loop, it was necessary to define a group of patients who had chosen this method. A study group from among the patients coming to the Buffalo Planned Parenthood Center between January 1, 1964 and July 1, 1964 was identified. Given a choice of contraceptives—i.e., orals, condoms, diaphragms, jelly, rhythm, and the loop—these women had selected the loop. After medical examination a loop was inserted, and the patients were asked to return annually for examination. Since 1964, some type of contact was made

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with 440 patients of the initial 500 who received loops. Using July 1, 1974, as a cut-off date, synthetic decrement life-tables for women utilizing the loops were calculated following the procedures described by Tietze (3). These tables summarize the experience of women using the loop during any segment of the 10-year study period. If a patient stopped using the loop for any reason, she was counted as a termination. Women who did not recommence the IUD during the study period were also counted as a closure.

Differences between events and closures have already been thoroughly discussed in the literature (4). For simplicity, this paper will focus on closure rates only.

Woman-Months of Experience

Although after five years 29.1% of patients had been lost to follow-up, by combining five years of experience with Loops C and D, 20,354 woman-months of experience were available for analysis. After 10 years, an analysis of 27,954 woman-months of experience was made, although 38.9% of patients were lost to follow-up for Loops C and D.

Age and Parity

At the beginning of the study, the mean age of a woman choosing to utilize the loop was 27.2 years. The average parity was 3.5. Table I gives the distribution of subjects by age and parity.

TABLE I

Percent Distribution of Age and Parity of Patients Accepting Loop C or D at the Buffalo Planned Parenthood Center in 1964

Age		Loops
15–19		6.2
20–24		31.0
25–29		30.5
30–34		19.8
35+		12.5
	Mean Age 27.2 years	100.0
Parity		
0		0.5
1		9.7
2		21.8
3		23.8
4		19.8
5+		24.4
	Mean Parity 3.5	100.0

Effectiveness

The net cumulative rate of closures for accidental pregnancies for Loops C and D increased from 1.5 per 100 women years after one year of experience, to 3.0 (per 100 women who entered the study) at the end of five years, and to 5.3 at the end of 10 years of observation. Figure 1 displays the fact that closures from accidental pregnancies continue to occur, even after 10 years. The curve does show a higher rate of accidental pregnancies during the first two years of use.

Expulsions

The net cumulative closure rates for expulsions of Loops C and D during the past decade are depicted graphically in Figure 2. The flattened curve of expulsions contrasts with the almost straight line phenomenon of accidental pregnancies seen in Figure 1. It begins to flatten after three years, indicating a decrease of expulsions after the first three years of use; in fact, there were no expulsions after the fourth year. Closure rates for expulsions amounted to 3.6 per hundred women at the end of one year, rising to 7.5 at four years. Even after 10 years of observation, closure rates for expulsions are unchanged at 7.5 per hundred women who entered the study.

An axiom of intrauterine contraception is that expulsions decrease with time.

NET CUMULATIVE CLOSURE RATE FOR ACCIDENTIAL
PREGNANCY - LOOPS C & D

AT BUFFALO PLANNED PARENTHOOD - 1964 - 1974

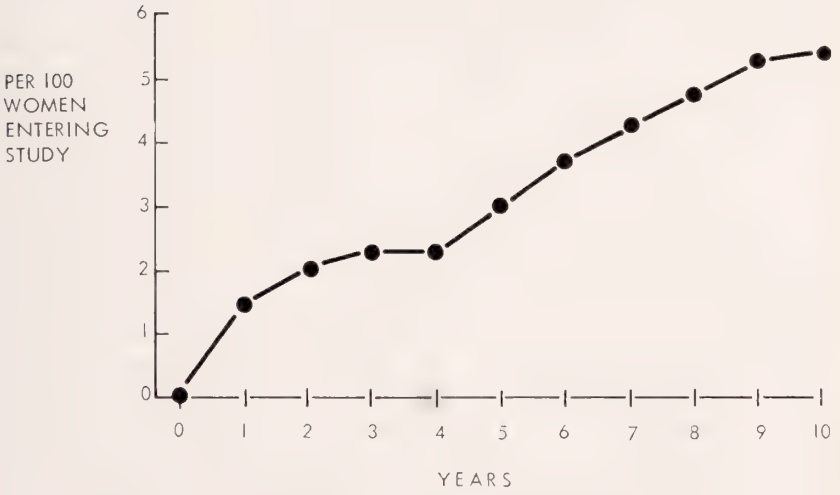


Figure 1.

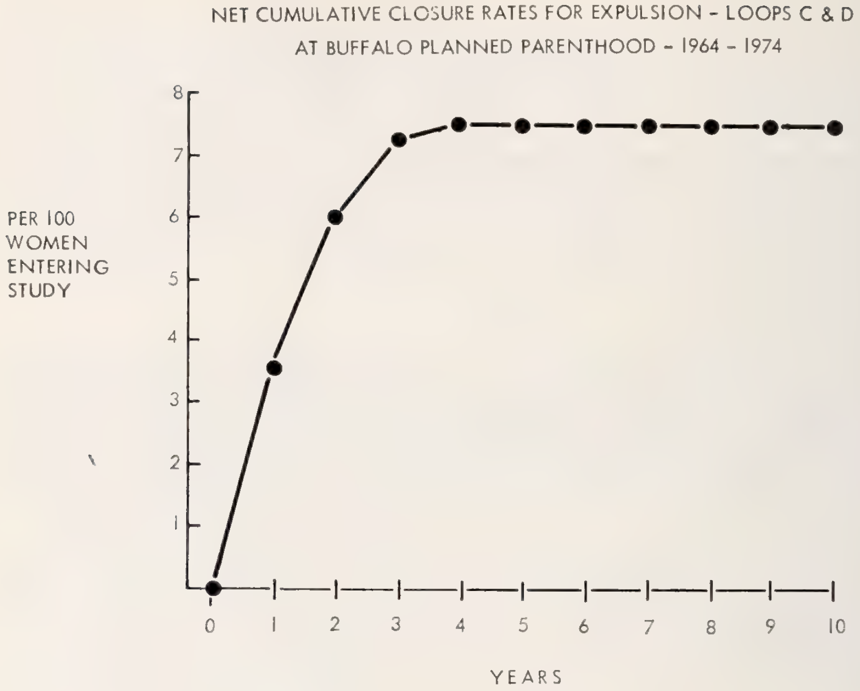


Figure 2.

Removals

Removals will be discussed as net cumulative rates of closure under the following headings: (a) Bleeding and/or pain; (b) Other medical reasons; (c) Planning a pregnancy; (d) Other personal reasons.

a. For bleeding and/or pain. Removals for bleeding and/or pain showed a rapid rise during the first two years of use. At the end of one year, 7.3 per hundred women entering the study removed the loop for this reason. At the end of two years, 14.4 per hundred women had discontinued the loop for bleeding. Over the next few years, the remaining patients apparently experienced less bleeding because at the end of five years, the net cumulative removal rate was 20.9. After 5 years, the cumulative rate of removals for bleeding was still increasing, but more slowly to a maximum of 26.8 at the end of 10 years. Over the decade studied, about one-fourth of the patients had discontinued the loop for bleeding and/or pain. Bleeding is always the most significant reason for discontinuation of any intrauterine contraceptive. It is especially difficult for patients to accommodate to the bleeding patterns in the first two years of use of an intrauterine device (Fig. 3).

b. Other medical reasons. These reasons include such things as leukorrhea, fear of harm, or the recommendations of the family physician. Occasionally the family doctor would advise the patient to have the IUD removed prior to abdominal surgery; for example, a cholecystectomy.

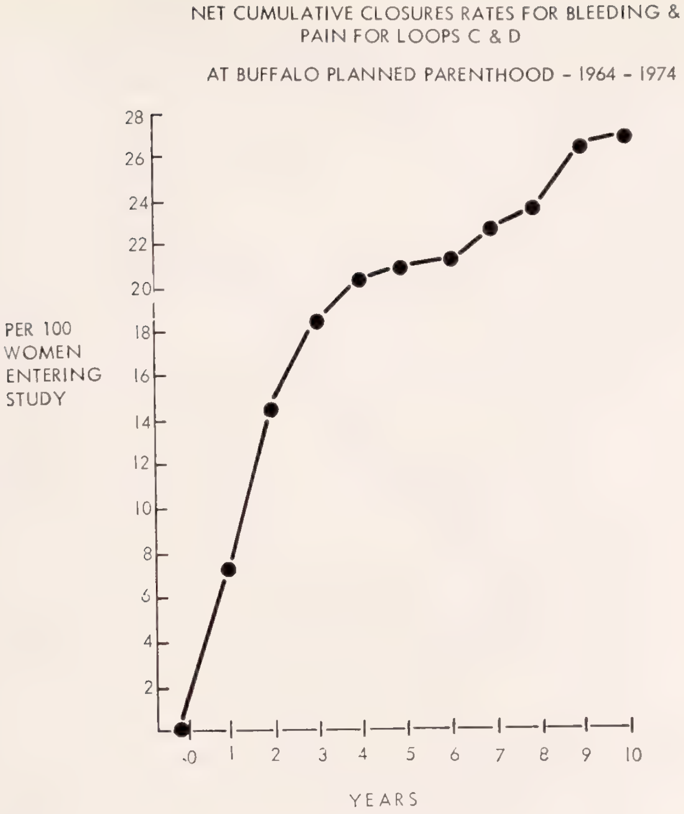
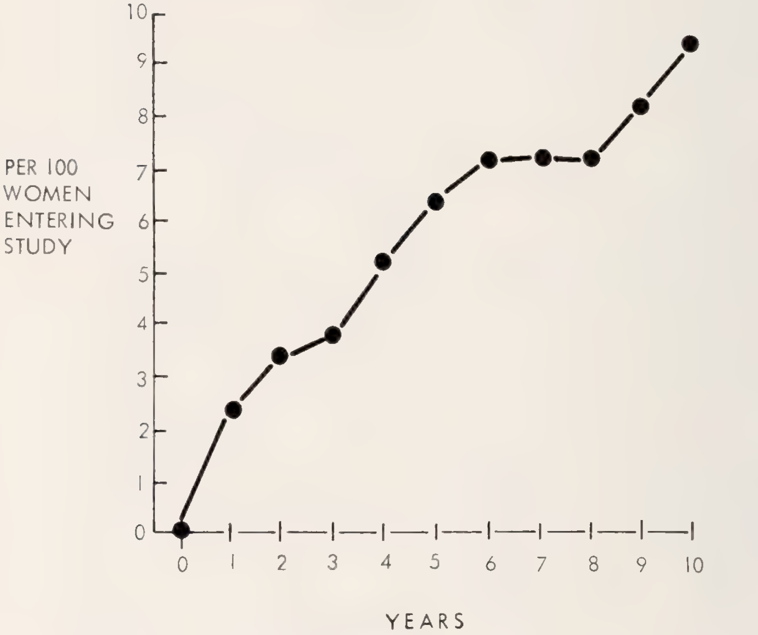


Figure 3.

Within the first year, 2.2 patients per hundred women had discontinued the loop for other medical reasons. After five years, this rate had increased to 6.3 and after 10 years, medical reasons accounted for 9.3 closures per hundred women. This phenomenon is displayed in graphic form in Figure 4. Although there is a slight flattening of the curve in the middle years, closures for medical reasons continue throughout the study and the phenomenon is best described as a straight line.

At the end of 10 years, the cumulative closure rate for medical reasons ranks third in significance for discontinuing the loop.

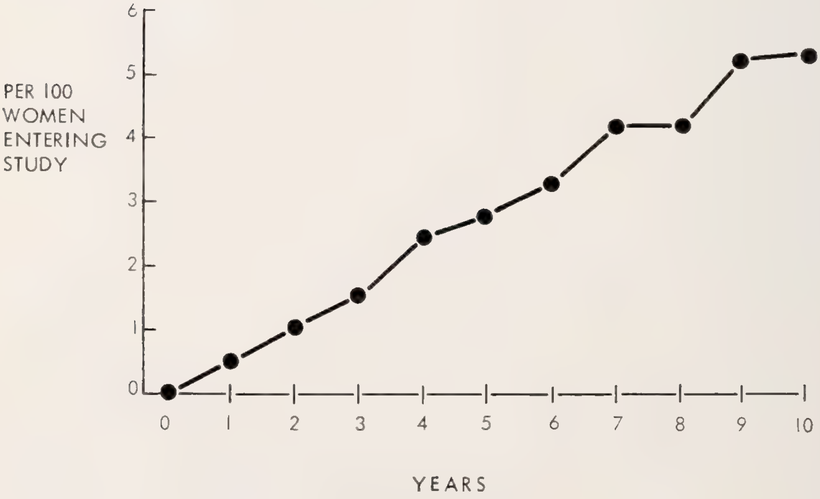
c. Planning a pregnancy. Rates of removals for planning a pregnancy distributed over time are depicted in Figure 5. The rate appears as a straight line, increasing steadily over the 10-year period. At the end of one year, 0.5 per hundred women years discontinued for this reason. At the end of five years, 2.9 per hundred women had discontinued the loop to plan a pregnancy. When 10 years had elapsed, 5.2 per hundred women had discontinued the loop for a planned pregnancy. Removal for planning a pregnancy remained the least significant reason for discontinuing contraception in this group of women. The rate of 5.2 who discontinued the loop for planning a pregnancy is very close to the



NET CUMULATIVE CLOSURE RATES FOR OTHER MEDICAL REASONS – LOOPS C & D

AT BUFFALO PLANNED PARENTHOOD – 1964 – 1974

FIGURE 4.



NET CUMULATIVE RATES OF CLOSURES FOR LOOPS C & D FOR PLANNING A PREGNANCY

AT BUFFALO PLANNED PARENTHOOD – 1964 – 1974

FIGURE 5.

5.3 who discontinued the loop because of accidental pregnancies. After 10 years of use it is a curious coincidence for removals for planning a pregnancy to be the same as the removals for accidental pregnancies.

d. Closures for personal reasons other than planning a pregnancy. Figure 6 reveals the cumulative rates of closures for Loops C and D for personal reasons, excluding planning a pregnancy, during the 10-year period under study. In rank, the second most important factor for loop closures is a nonmedical, personal reason. After one year of observation, 0.5 patients per 100 women had discontinued the loop for personal reasons. This closure rate slowly rose to 4.0 at five years and then increased sharply during the next five years to a cumulative rate of 13.1 per hundred women. This marked increase in closure rates for personal reasons between the fifth and the tenth year of use is unique because no other rate for discontinuation accelerated during the second half of the decade under study.

Why did this accelerate? Personal reasons, such as widowhood, divorce, separation and infrequent intercourse correlate positively with time. This means

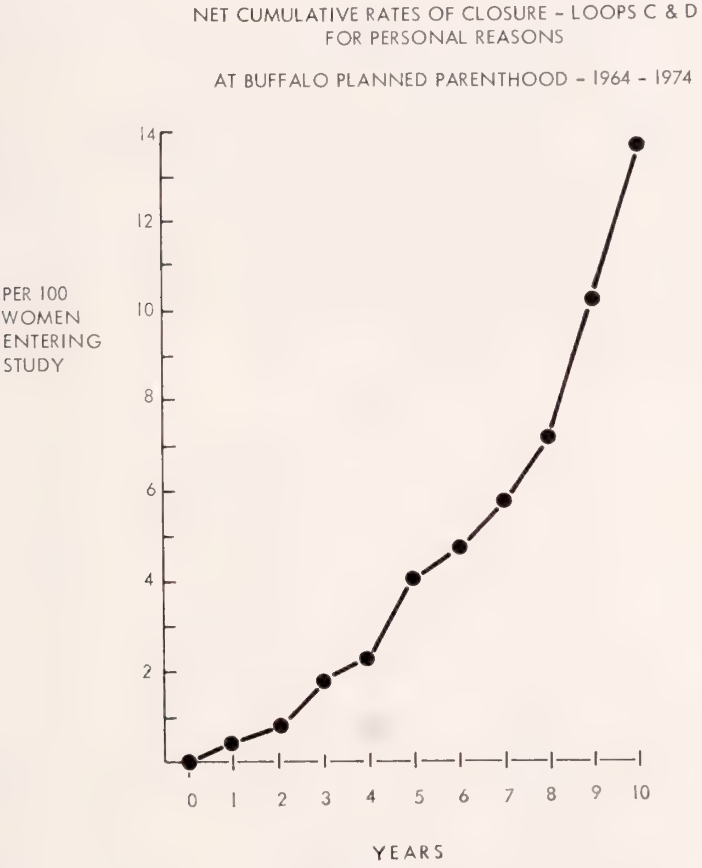


FIGURE 6.

there were more divorces, separations, and widowhood in the second half of the decade. Another interesting phenomenon which accounted for this acceleration is the fact that in the first half of the decade women tolerated spotting and discharge which accompanied IUD usage, so long as there was no attractive alternative. Beginning in 1968 and 1969, laparoscopic sterilization became available. This was another one-time procedure which afforded years of protection. It was an attractive alternative to the IUD, because it eliminated spotting and discharge for which the IUD was sometimes responsible. Thus elective sterilizations added to widowhood, etc., accounts for the accelerated discontinuation of the IUD for personal reasons in the second half of the decade.

Continuation Rate. The continuation rate shown in Figure 7 is a curve which flattens with time. After one year of experience, 84.4 per hundred women continued to utilize the loop. This decreased to 53.1 per hundred women persisting in the use of the loop at the five-year interval. At the end of 10 years of observation continuation was 32.8 per hundred women entering the study. Thus, approximately one-third of the women who chose the loop in early 1964, were still wearing the loop in 1974.

Alternative Choices following Loop Closures. During the summer of 1974, 111 patients who had discontinued the loop and chosen another contraceptive were contacted for information about their alternative choices. These are listed in

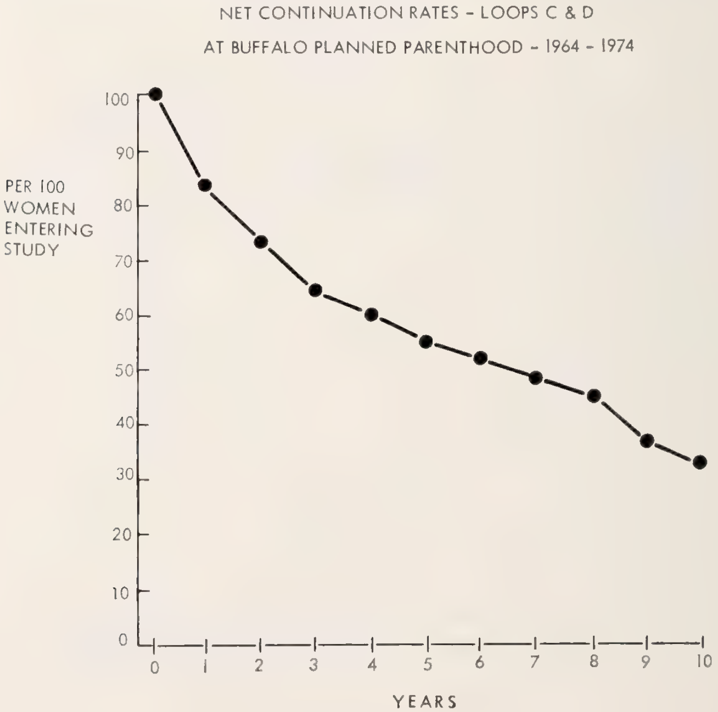


FIGURE 7.

order of importance in Table II. In order of popularity, the first choice was oral contraception, followed by the diaphragm, tubal ligation, hysterectomy and a different IUD. Condoms were not a popular alternative. Vasectomy was equally unpopular. Men were not eager to practice birth control.

After analyzing the distribution of each second choice over time, it is possible to discern if the distribution of an alternative differs from the expected distribution of total terminations over time. (See Table III).

Of the 41 closures choosing the pill as their second choice, 63% selected pills during the first two years and 20% during the third and fourth years. Because 17% opted for oral contraception between 1968 and 1971 the distribution pattern flattens rapidly. Interestingly, no patients who terminated loop use between 1972 and 1974 chose oral contraceptives, a distribution different from the expected.

The distribution over time of those choosing the diaphragm, appears similar to the expected distribution for all second choices.

Tubal ligations show a different time distribution. As shown in Table III, 50% of them occurred during the last two and one-half years of our study. The reason

TABLE II

Second Choice of Fertility Control by Women Who Discontinued Loops C, D Between 1964 and 1974

2nd Choice After Loop	Number	Per Cent
Orals	41	37.0
Diaphragm	28	25.2
Tubal Ligation	14	12.6
Hysterectomy	13	11.7
Other IUD	11	9.9
Condom	2	1.8
Vasectomy	2	1.8
	—	—
Total	111	100.0

TABLE III

Distribution of Second Contraceptive Choices by Year

	Orals		Diaphragm		Tubal Ligation		Hysterectomy		Another IUD		Condom		Vasectomy		All Second Choices	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
64–65	26	63	16	57	2	14	4	31	2	18	2	100	—	—	52	47
66–67	8	20	4	14			4	31	3	27	—	—		—	19	17
68–69	2	5	4	14	3	22	4	31	5	46	—	—	—	—	18	16
70–71	5	12	1	14	2	14	—	—	—	—	—	—	1	50	9	8
72–74	—	—	3	11	7	50	1	7	1	9	—	—	1	50	13	12
Total	41	100	28	100	14	100	13	100	11	100	2	100	2	100	111	100

is the advent of laparoscopy, which permits female sterilization to be a one-day event, with little convalescence. As an alternate method to the loop, sterilization by laparoscopy appears to replace oral contraception during the past two and one-half years.

The number of hysterectomies during the first five years reflects an attitudinal change; it was considered by some to be a reasonable method of fertility control in the 1960's. A change in this medical attitude is shown by the single hysterectomy performed between 1970 and 1974. More hysterectomies would have been expected in the second half of the decade because patients in the study were older. When the number of hysterectomies and tubal ligations are added, it is evident that women in this study group had greater interest in terminating fertility than in child-spacing. Furthermore, the eagerness with which women seek sterilization or use contraceptives compared to their male partners is impressive.

Final Comments

At the Buffalo Planned Parenthood Center between January and June of 1964, 440 patients out of 500 who chose Loop C or Loop D as a method of contraception were subsequently contacted. These women were followed for a 10-year period, during which 171 patients or 39% were lost to follow-up.

The reasons for closures at five and 10 years are compared in Table IV. Both at the five-year mark and at the 10-year mark, bleeding and/or pain were the primary reasons for discontinuing the loop.

However, the second reason for discontinuing the loop changed in the last five years. During the first five years, expulsions accounted for 7.5 closures per hundred women who entered the study. At the decade interval, personal reasons accounted for 13.1 closures while expulsion continued at 7.5 per hundred women. Third in rank at five years, medical reasons amounted to 6.3, which increased to 9.3 per hundred women at the tenth year. During the first five years, personal reasons took fourth place, whereas expulsions took fourth place at the tenth year.

Accidental pregnancy and planning a pregnancy were the least significant reasons for closures after either the fifth or tenth year.

After 10 years, the overall order of significance for all alternatives, places the

TABLE IV

Order of Reasons for Closures for Loops C and D at 5 Years and at 10 Years per 100 Women Entering Study

5 Years		10 Years	
Bleeding and Pain	20.9	Bleeding and Pain	26.8
Expulsions	7.5	Other Personal	13.1
Other Medical	6.3	Other Medical	9.3
Other Personal	4.0	Expulsion	7.5
Accidental Pregnancy	3.0	Accidental Pregnancy	5.3
Planning a Pregnancy	2.9	Planning a Pregnancy	5.2

orals as the most popular, diaphragms second, and tubal ligation third. (See Table II).

A change in the pattern of loop alternatives is revealed when the second choices over time are plotted. In the early years, patients tended to choose oral contaceptives, while in the later years laparoscopic tubal ligation became the preferred method. Of those who changed to oral contraceptives, 63% did so during the first two years, 83% during the first four years. Of those choosing sterilization, 50% did so between 1972 and 1974, while only 14% did so between 1964 and 1967. The reason for this was changing technology. In late 1969 and early 1970, laparoscopic sterilization became readily available in most hospitals in western New York. It allowed women the important alternative of terminating childbearing. Technology can change the patterns of fertility control and contraceptive practices.

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"And So On"

RONALD J. PION, M.D.

> ----, their country was by far the richest and most powerful country on the planet. It had most of the food and minerals and machinery, and it disciplined other countries by threatening to shoot big rockets at them or to drop things on them from airplanes.
>
> Most other countries didn't have doodley-squat. Many of them weren't even inhabitable anymore. They had too many people and not enough space. They had sold everything that was any good, and there wasn't anything to eat anymore, and still the people went on f-----g all the time.
>
> F-----g was how babies were made.
>
> A lot of people on the wrecked planet were communists. They had a theory that what was left of the planet should be shared more or less equally among all the people, who hadn't asked to come to a wrecked planet in the first place. Meanwhile, more babies were arriving all the time—kicking and screaming, yelling for milk.
>
> In some places, people would actually try to eat mud or suck on gravel while babies were being born just a few feet away.
>
> And so on."
>
> *Breakfast of Champions*, Kurt Vonnegut, Jr. (1973)

It is 1975, and this rich, powerful country is not an example of a contracepting society. Nonprescription contraceptive products are not marketed freely. There are no radio and television commercials advertising condoms, foams, jellies, and creams. Neither the Avon lady nor her closest competitor carries such items in her "consumer line." The products do not appear in Sears' mail-order catalogue or in the discount listings of the drugstore advertisements placed daily in our newspapers.

Our health care system (non-system that it might be) perpetuates the myth that there *really* are male and female methods, and that the pill and the intrauterine device are the most effective methods developed to date.

Arbitrary assignment of sex specificity inhibits method adoption by potentially responsible couples. Were satisfying noncoital sexual practices encouraged and substituted at the time of suspected ovulation, pregnancy need never occur even in the absence of a responsive health care system.

It is rather paradoxical that at a time when medical "person power" shortages are being decried and the cost of medical care is rising, family planning activities are being added to a long list of "priority" medical responsibilities. Most people interested in avoiding pregnancy as a consequence of sexual intercourse do not need doctors, their associates, or cumbersome institutions. They do require relevant, easy-to-comprehend information that will provide a rational basis for choice and permission to exercise such choice.

Diaphragm-fitting rings could be made available in drug stores and super-

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markets, and could be accompanied by suitable pictorial, FDA-approved inserts that facilitated proper sizing either by the male partner of the woman, or by the woman herself. Certainly, the motivation for performing the procedure correctly is highest in the user(s). Should difficulty be experienced during an attempted fitting, the insert could advise seeking physician or clinic consultation. A discount coupon present within the ring set could be used towards the purchase of the "color-matched" diaphragm. The latter would, of course, contain spermicidal agents along with easy-to-understand directions for use. A simple description of the "rhythm" method could be included so as to enhance the efficacy of this or any other COUPLE method in preventing an unplanned conception.

All appropriate methods might carry the simple message that *menstrual delay may be an early sign of pregnancy. Should this occur, by all means see your physician one week after your miss period.*

Pregnancy tests could be offered as over-the-counter items for couples anxious to avoid a pregnancy and to those seeking to start one. This practice might enhance earlier entry into our confusing health system. False negative and or false positive results could be explained by suitable diagrams, and the purchaser again advised to seek medical follow-up for needed clarification. Warnings could even be issued to protect an overly sensitive manufacturer's legal standing.

Preconceptional methods of fertility control (conception avoidance) require postconceptional methods of fertility control (birth avoidance) as back-up if the process is to be "fail-safe." Postconceptional methods require prevention of a fertilized egg implantation or early removal or destruction of an implanted fertilized egg. The technology exists at present to induce a delayed menstrual period—hormonally if the woman is not pregnant, and mechanically if she is. In the latter instance, the procedure properly must be termed an early abortion. It should be noted however, that the instrumentation required during the first 7–14 days after a missed period is significantly different from that used for later first trimester pregnancy termination. This significant difference could be reflected more universally by decreased costs and altered prerequisites.

Arguments persist within the medical community about whether a mechanical method should be employed at a time when the diagnosis of pregnancy is uncertain. Many of those opposed to such "meddlesome" practices have for years utilized surgical means for diagnostic purposes, and have not been apologetic when the suspected diagnosis had not been confirmed. Dilatation and curettage has been performed for decades in order to rule out endometrial neoplasia and other suspected pathology, and when not confirmed, the physician did not apologize for the "unnecessary" procedure. Why should a physician apologize or have to defend aspirating the uterus of a woman "sick with anxiety" over the possibility of a suspected pregnancy, whether the aspiration confirms the suspicion of pregnancy or not?

If we were truly concerned with planned conception in these United States, our governmental centers responsible for the collection of vital statistics would reflect this. Birth and abortion certification would contain confidential material describing whether the particular pregnancy began as a planned or unplanned occurrence. The woman could be asked if she or her partner used a method of contraception during the month she conceived. If her answer were yes, the specific method would be noted and perhaps a failure rate calculated. If her response were no, she could be questioned as to whether she and her partner would have preferred for her to have conceived earlier or later. In the former instance, the couple could be tagged as a possible subfertile unit and referred to appropriate resources in the future. In the latter instance, one might assume that the particular pregnancy in question was unplanned. Periodic sampling of such data could yield more complete information about our family planning programs than the current data provide. At present, most programs look at the population seen in clinics, excluding by that very process those who do not attend. The high-risk group is the one with the unplanned conception, more easily identifiable when pregnant—at the time of delivery, abortion, or during prenatal care.

Finally, were we to emerge as a contracepting populace, products such as sanitary napkins and tampons could serve as vehicles of information. Since most females begin to menstruate at or about 12 years of age, and since most conceptions do not occur until after approximately age 17, there are 5 years during which we might educate young women about conception control by providing pictorial information as package inserts. The following three messages might be considered for inclusion.

(1) How not to become pregnant if you are not interested in raising a child.
(2) How to determine if you are pregnant so that you may decide whether to continue the pregnancy.
(3) How to increase the likelihood of your producing a healthy infant if you are anxious to consider child rearing.

The suggestions offered may or may not improve the quality of services for those interested in utilizing them. We could find out if it were important —And so on!

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Prostaglandins in Conception Control

HAROLD SCHULMAN, M.D.

Accelerating basic and clinic research in the past few years is demonstrating that prostaglandins play a fundamental role in myometrial function (1). Appropriate administration of this drug will excite the uterus from its resting state, leading to the onset of labor and expulsion of uterine contents. This arousal can be accomplished at any time in human gestation after implantation has occurred. The physiologic mechanism is so fundamental, that it appears that prostaglandin inhibitors may have a role in the prevention of undesired or premature labor (2), provided only that inhibitors will prove not to be detrimental to the fetus.

Chemistry and Pharmacology

Prostaglandins are 20 carbon chain fatty acids which are ubiquitous throughout the body (Fig. 1). The compounds of importance in reproduction appear to be prostaglandins of the E and F type. These two compounds differ in that prostaglandin E has a ketone group on position 9, whereas prostaglandin F has a hydroxyl group at the same position. A prostaglandin subscript of 2 or 3 refers to the number of double bonds present. The compounds are metabolized primarily at position 15; therefore, potentiation of the drug can be achieved by attaching a methyl group to position 15. Other chemical techniques for potentiating the drug's action have included attaching organic groups to position 16 or altering the acidic carbon 1 to a methoxy group. These alterations in structure have been pursued vigorously because of the undesirable side-effects of the primary prostaglandins.

The effects of prostaglandins can be seen on vascular and nonvascular smooth muscle, and the central nervous system. Hence, common side-effects are flushing, headache, pallor, coldness, hypertension and hypotension, nausea, vomiting, diarrhea, bronchospasm and cough, hyperthermia, chills, and drowsiness. The differences in action of prostaglandin F (Pg F) and prostaglandin E (Pg E) on the myometrium will be demonstrated by the clinical studies we have performed.

The vascular effects of Pg E may be important in the regulation of uterine blood flow. Since Pg E acts to produce vascular smooth muscle relaxation, there may be a deficiency in endogenous circulating Pg E in conditions such as toxemia of pregnancy (3).

It appears that there may be a minute amount of prostaglandin synthesis going on at all times; flooding the reaction with a precursor, arachidonic acid, results in a significant increase in measurable prostaglandin (4). This is useful

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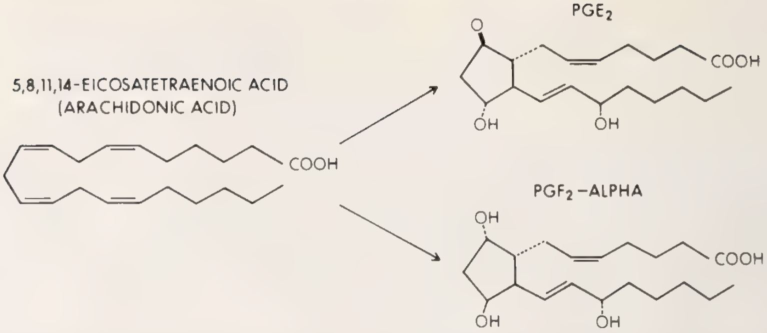

FIG. 1. Chemistry of prostaglandin E and F. Arachidonic acid is the precursor for these 20 carbon chain fatty acids. Numbering occurs from right to left. Prostaglandin E has a ketone group at position 9, and Pg F has a hydroxyl.

because it provides an avenue through which one can elicit natural production of prostaglandin and avoid exogenous drug stimulation.

There seem to be two levels at which prostaglandins affect cells. Membrane receptors have been identified, which may be the mechanism by which immediate drug action can be explained. However, most or all cells have the capacity to synthesize prostaglandins, and it is believed that this is their "natural" area of functioning. Cyclic adenosine monophosphate (cyclic AMP) is the key intracellular mediator which drives the cell to perform its unique activities. Prostaglandins appear to be additional intracellular regulators which exert their actions through increasing or decreasing cyclic AMP activity (5).

Material and Methods

Since 1972, a clinical team in the Department of Obstetrics and Gynecology at the Albert Einstein College of Medicine has had the opportunity to study several prostaglandin compounds and their effects on human pregnancy.* The results of our study demonstrate how clinical investigation, based on a theoretical framework, can help elucidate the mechanism of action of a drug, provide guidelines for clinical use of a drug, and point the way to new directions for research.

The theoretical framework which we adopted was proposed by Dr. Arpad Csapo (6). His concept was that the pregnant uterus is in a state of inhibition of contractility, and the onset of labor results from the release of this inhibition. Of extreme importance in this concept is that the uterus has the capacity to expel its contents at any time, but is prevented from doing so by some mechanism or substance. It was suggested that this "braking substance" is progesterone, which is created by the maternal-placental endocrine unit, and modified by the feto-placental unit.

Women between 8–20 weeks gestational age (Nagele) desiring termination of pregnancy were selected for this study (7). A catheter was inserted into the uterus either transvaginally or transabdominally for continuous recording of intrauterine pressure. The following end points were then measured:

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* This team has consisted of Drs. Chin-Chu Lin, Luis Saldana, Theodore Leibman, Wu Hsiung Yang, Tahsiung Tsai, Misses Georgia Randolph and Maryanne Cunningham, and the author.

1. Oxytocin response (OT). An intravenous bolus of 1,000 milliunits of oxytocin was given to test the state of reactivity or inhibition of the uterus. This was recorded in terms of active pressure response (AP) (Fig. 2).

2. The prostaglandin was administered and the response measured in terms of intrauterine active pressure (AP) and resting pressure (RP). In this way a dose-response relationship was established.

3. Progesterone metabolism was estimated by serial measurement of plasma progesterone, and by assay of placental progesterone at the time of abortion.

4. Clinical efficacy was reported in terms of instillation to abortion time (IAT) or instillation to delivery time. Side-effects were recorded to appraise clinical usefulness or tolerance.

Summary of Results

Intraamniotic Pg F_{2a}. The first study was performed with intraamniotic Pg F_{2a}. An initial group of 20 women, 15.9 ± 0.6 weeks pregnant, of 1.4 ± 0.4 parity, were given Pg F_{2a} intraamniotically starting with a 20 or 25 mg dose. If an adequate uterine pressure response was achieved and oxytocin conversion was seen (higher active pressure, AP) on a second challenge test (OT #2) at 90–120 minutes, it was assumed that the uterus was now reactive. Uterine activity would be maintained with oxytocin 50 mu/min intravenously, and it was assumed that delivery inevitably would occur. This assumption proved to be valid, because the 20 women aborted in 16.5 ± 2.1 hours with an average total dosage of 24.3 ± 1.1 mg (8).

The average maximum pressure responses achieved from the Pg F_{2a} in this

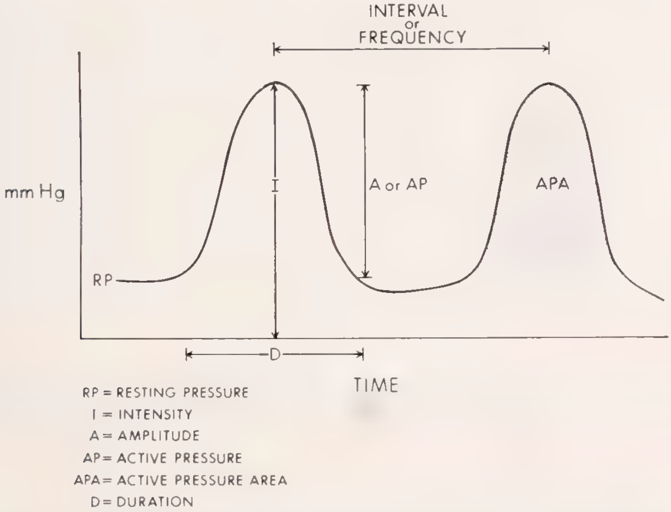

FIG. 2. Idealized uterine pressure curves. Resting Pressure or RP and Active Pressure or AP are useful measurements for evaluating mechanism of action of prostaglandins.

series were then utilized as guidelines or criteria for management of additional patients. When a dose of Pg F_{2a} was given, it was expected that certain pressure responses would have to be achieved for successful outcome. If these responses were not noted, additional drug was given at 90-minute intervals until such pressure responses were recorded. This approach was extended to 30 additional patients with identical results.

When a study is carried out utilizing a dose-response relationship and time of an event (abortion) as a variable, the paradoxical result is that patients receiving the smallest dose had the earliest response whereas larger doses were required for those taking the longest time to abort. However, in this way, a precise dosage can be derived. For intraamniotic Pg F_{2a}, this was an average dose of 25 ± 1.1 mg, or a dose of 41 mg to successfully abort 96% of the population within 17.4 ± 1.2 hours. The cumulative abortion rate at 24 hours with the prostaglandin-oxytocin approach was 78%.

We confirmed that the abortion process is accompanied by a decline in plasma progesterone, and work in our department has demonstrated a significant decline in placental progesterone. Since time of abortion correlated with rate of progesterone decline, this represented supportive data for Csapo's concept that initiation of labor required a fundamental alteration and decrease in placental function.

Intraamniotic Pg F_{2a} had a unique effect on the uterus not seen previously with other drugs. Shortly after injection, there was a slow, steady rise in resting pressure with gradual development of superimposed cyclic active pressure (Fig. 3). In contrast to the effects of other drugs, the uterus maintained a resting pressure of 40 mm Hg, indicating that active relaxation or accomodation of the smooth muscle fibers did not occur. Initially, it was assumed that this response was important to the effect of the drug on the uterus, since elevation of resting pressure profoundly interfered with uterine blood flow.

Extraovular Pg F_{2a}. The same approach was then used for termination of pregnancy in the 13-15 week period. A catheter was inserted into the uterus through the cervix for simultaneous measurement of pressure and injection of drug (9). Twenty women of 13 ± 0.3 weeks gestation were aborted in 17.9 ± 2.9 hours with 11 ± 1.8 mg Pg F_{2a}. The 24-hour cumulative abortion rate was 83%. Again, using a measured dose-response relationship, a predictable outcome was achieved. Of importance both in the intraamniotic and extraovular group were the presence of prostaglandin side-effects in 25-70% of the women. Also distressing was the high incidence of retained placentas. Approximately one-third of the women required active intervention to remove the placenta, whereas in our experience

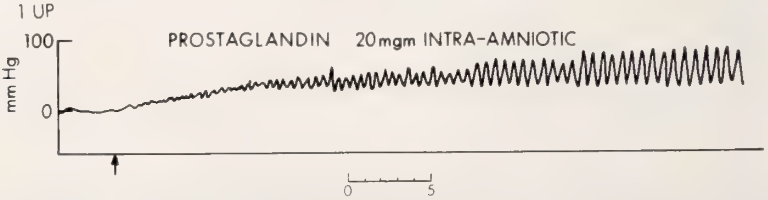

FIG. 3. Effect of Pg F_{2a} on intraamniotic uterine pressure (IUP). Note gradual sustained rise in resting pressure with superimposed increasing cyclic active pressure.

with hypertonic saline amnioinfusion, this was necessary only 10–15% of the time.

Intramuscular 15-methyl-Pg $F_{2\alpha}$. An intramuscular preparation of Pg $F_{2\alpha}$ was synthesized by attaching a methyl group to the 15 position. The clinical trial was interesting theoretically but unacceptable to us as a therapeutic method (10). In the dosage employed, 250 μg, there were striking elevations of resting pressure and cyclic active pressure, but abortion did not inevitably ensue. This was supportive of Csapo's concept that labor or abortion does not occur because of uterine contractions, but that something more fundamental must occur before the uterus is able to expel its contents. Side effects occurred in virtually all women, making this approach clinically unacceptable when compared to the intraamniotic method.

Vaginal suppositories of Pg E_2. Prostaglandin E_2 differs from Pg $F_{2\alpha}$ in that it relaxes vascular smooth muscle, bronchioles, and circular smooth muscle fibers of intestine. Since the uterus contains longitudinal and circular fibers, it is possible that Pg E_2 may exert a dual effect on myometrium, e.g., constrictive to longitudinal fibers but relaxing to circular fibers. This method has met with good success in several centers but side effects occurred in approximately 75% of women. After a control study with the free suppository, we began inserting the suppositories into the lid of a contraceptive diaphragm in the hope of reducing side effects, diminishing dosage, and increasing efficacy (11). The results have been dramatic. In 110 women of 1.45 ± 0.17 parity, of 15.4 ± 0.3 gestational weeks, receiving an average total dose of 78.3 ± 0.12 mg, the mean abortion interval was 14.12 ± 0.7 hours. Uterine pressure tracings revealed that this approach initiated normal uterine contractions without accompanying elevations of resting pressure (Fig. 4). This resulted in reduced retained placenta rates and offered promise as a

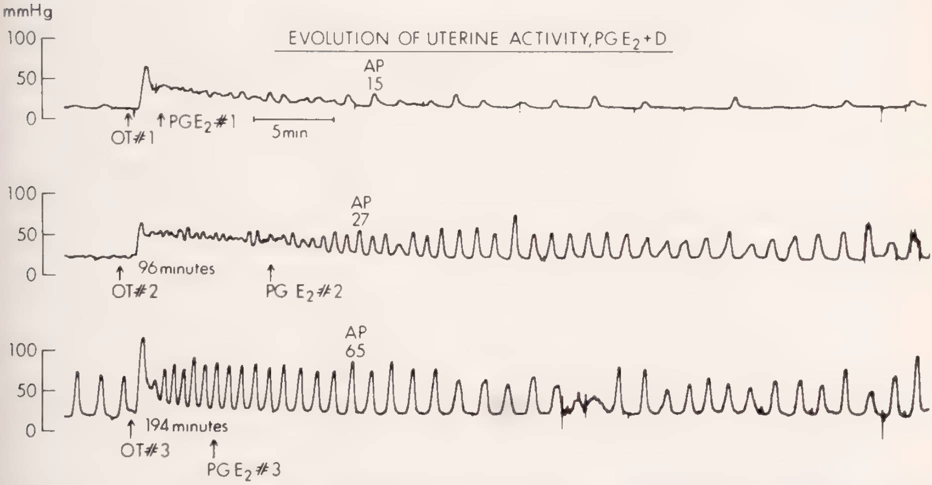

FIG. 4. Uterine activity with intravaginal prostaglandin E_2 suppositories administered in a contraceptive diaphragm. Note gradual evolution of normal uterine activity without elevation of resting pressure. Note alteration in oxytocin responsiveness (OT #2) at 96 minutes despite absence of preceding uterine activity. OT = maximum active pressure of oxytocin testing; D = diaphragm.

compound which would be useful for induction of labor. We and others have also shown that this compound can induce first trimester abortions.

Induction of term labor. Pg $F_{2\alpha}$ and Pg E_2 administered in various ways, i.e., oral, intravenous, vaginal, and extraovular, have not resulted in results superior to intravenous oxytocin in the term pregnancy. The principle obstacle to achieving 100% success may be that the term or near-term uterus has such a large mass of reactive myometrium that it is not possible inevitably to overcome placental resistance without creating elevations in resting pressure which are dangerous to the fetus (12).

Discussion

The discovery, synthesis, and basic clinical research on prostaglandins has been an exciting, swiftly moving story. The outline of the story seems to have already been written, and what remains to be done is to fill in the details.

Prostaglandins are ubiquitious substances probably present in all cells and participate in the regulation of the cell's activity. The fact that exogenous prostaglandins are luteolytic when administered to primates indicates that in some circumstances they can interfere profoundly with cells which function to produce progesterone. The human placenta contains a 15-hydroxy-prostaglandin-dehydrogenase, and it has been demonstrated that rat placentas vary in their ability to metabolize prostaglandins as gestation proceeds (13).

Progesterone withdrawal appears to be accompanied by activation of prostaglandin synthesis. Luteectomy in the rabbit (progesterone withdrawal) leads to the onset of labor, but this can be delayed by a prostaglandin antagonist, naproxen. Hence there is considerable indirect evidence suggesting an intimate relationship between prostaglandins and progesterone, but the exact interaction remains to be elucidated.

Csapo believes that the method by which prostaglandins initiate labor is through their effect on arterioles and capillaries. The primary effect may be vasoconstrictive, leading to diminution of blood flow and eventual decrease of placental function, resulting in release of hormonal inhibition and initiation of labor (14).

Women seeking abortion provided an opportunity for the study of uterine control in human pregnancy. Our work and studies upon animals and human subjects permit several generalizations to be made. Prostaglandins are most effective when placed into or near the uterus (14, 15). In the human, this would imply intraamniotic, extraovular, or paracervical administration. Intravenous or intramuscular routes of delivery are less predictable and introduce an incidence of side effects which is probably unacceptable to most. Since prostaglandins are physiologic compounds, they offer the promise of being an abortifacient with minimal material risk. The hypertonic saline amnioinfusion technique for second trimester abortion probably has an irreducible maternal death risk of 10 per 100,000 cases. This risk exists because the hyperosmolar solution produces tissue necrosis which may result in infection and defibrination from release of decidual thromboplastins. Infection and defibrination are potentially lethal and uncontrollable complications (16).

Prostaglandins as a means of inducing labor near term still offer considerable challenge. Prostaglandin F_{2a} can produce significant and prolonged elevations of uterine resting pressure and therefore present too much risk for the fetus. Prostaglandin E_2 may be a better choice, but experiences with this compound given orally and intravaginally suggest that it is not superior to intravenous oxytocin. Although the mechanism of action of prostaglandins is significantly different from oxytocin, the biophysical properties of the term uterus have prevented the delivery of adequate dosages of Pg E_2 to inevitably convert the uterus into labor. It may be necessary to concentrate on techniques for enhancing prostaglandin synthesis. This can be and has been accomplished by inserting arachidonic acid, a prostaglandin precursor, into the amniotic sac (4). Unfortunately arachidonic acid could be an extremely toxic compound for the fetus.

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Advances and Opportunities in Fertility Research

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Contraceptive development depends on the understanding of physiologic mechanisms concerned with conception, basic studies in animals and human subjects to establish effectiveness and safety factors, and acceptability studies under various social and cultural circumstances. The total process is lengthy and complex, so that any new methods likely to emerge in the near future must now be at some advanced stage in the development process. Certainly, some testing in human subjects must have begun. Based on these criteria, the following "new" or "modified" contraceptives may be developed within the next 3 5 year period.

Methods for Use by Men

A combination-steroid method to arrest sperm production, based on oral, injectable, or subdermal implant routes of administration. Tests in men have established that it is possible to suppress sperm production while maintaining normal levels of plasma testosterone, and that this procedure is readily reversible (1). From here, work has to proceed in two directions: (1) applied research and development to select the best combinations of progestin and androgen among those now available, and the best routes of administration; and (2) basic study in animals and humans on various issues of safety and potential side effects.

Arrest of sperm production by trimonthly injections of progestin or androgen. At least three compounds have been tested in small numbers of men and proven to suppress spermatogenesis. The potential problems are a loss of libido or development of gynecomastia when progestins are used, and medical anxiety over metabolic disorders or cardiovascular hazards when potent androgens are used. Yet this approach is sufficiently promising to warrant the study of several synthetic steroids and their esters for spermatogenesis-inhibition free of unacceptable side effects (2).

An anti-androgen to prevent epididymal sperm maturation, based on oral or subdermal implant routes of administration. Tests in a limited number of men have been started, based on an observation made in rats given an anti-androgen by subdermal implant (3). In those studies, epididymal sperm failed to achieve the motility that occurs normally, and the animals were rendered infertile without loss of libido. Although the subdermal implant route of administration may not be feasible in men to achieve systemic activity via the circulatory system, the possibility of local action by implants placed in the scrotum contiguous with the epididymidis cannot be ruled out.

Reversible vas occlusion. Currently under clinical study are several removable

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clips that can be applied to the vas deferens through a small scrotal incision (4), and at least two devices which, by a more complicated procedure, can be placed within the vas. One of these is a simple plug made of polyethylene which is designed for subsequent surgical removal, if desired. The other is a micro-valve intended to be left permanently fixed within the vas, with a simple manipulation making it possible to place the valve in either an open or closed position, as desired (5). No fully satisfactory clip method has yet emerged; those tested until now either fail to close the vas or cause necrosis of the underlying tissue (6). Plugs so far tested have the same disadvantages.

Intra-vas device. An effort to cause sperm necrosis or immotility by placement of a nonocclusive foreign body in the vas deferens has been tested clinically, with only partial success (7, 8). In this first experiment, involving close to one thousand volunteer subjects, surgical silk was suspended within the lumen of the vas and fixed loosely to the perivasal surface to facilitate subsequent removal. Now experimentors are beginning trials with pharmacologically active intra-vas foreign bodies, including copper or zinc filaments. The effect of these metal ions in animals is to immobilize sperm or to cause head-tail separation. The first tests in men are based on observing these morphologic characteristics in ejaculated spermatozoa. Even if these trials are successful, it will be some time before contraceptive effectiveness tests could begin, since difficult issues of teratology are involved when there is a possibility of partial damage to sperm.

Methods for Use by Women

Long-term injectable progestin. Two compounds have been sufficiently used to have been marketed as trimonthly contraceptive injections in some countries (9, 10). They work by suppressing peaks of luteinizing hormone release, thereby preventing ovulation. Bleeding patterns with each compound are erratic. Most women, after experiencing irregular bleeding at first, tend toward amenorrhea. For each compound, important issues regarding safety still are unresolved. With increasing level of use, these questions should be answered within three years. Meanwhile, searches for other compounds that can be used safely as injectable contraceptives and for delivery systems that will provide slow and constant release of progestins from the site of injection are proceeding (11, 12).

Subdermal implants of progestin. This new method of contraception has been proven effective for periods of at least one year (13, 14), and is in the stage of product development. In its present form, the method requires the subdermal insertion and removal under sterile conditions of Silastic tubes or rods containing the anti-fertility hormone. Several progestins have been tested but the optimal compound has not yet been selected. Meanwhile, clinical trials are proceeding with eight different compounds, involving the use of one to six implants.

Intra-vaginal ring containing progestin. Comprehensive work has been completed to establish that the absorption of progestins through the vaginal mucosa can be used as the basis for ovulation suppression (15). The contraceptive effectiveness and acceptability of a product based on this principle are now being studied in field trials; three different progestins are under investigation. The compounds are incorporated into Silastic and molded into the form of a ring, similar to the size and shape of the rim of a vaginal diaphragm. The ring can be inserted by a woman and left in place one month or longer. Studies are proceeding on the basis of leaving the ring in place for one month, for two months, or for the (entire) interval between spontaneous bleeding periods. This new method is undergoing product development, with engineering and design modifications in progress to reduce cost and to standardize monthly steroid-release rates.

Contraceptive bracelets containing progestins. Absorption of steroids through the skin, a principle long-employed for cosmetic purposes, is now being tested as the basis for contraception. The present preliminary tests in women involve the use of Silastic as the carrier of progestin, in the form of a snugly-fitting arm bracelet (16). The clinical tests are being carried out with three different compounds and with two different forms of Silastic bracelets. The work needed to develop the contraceptive bracelet is mainly of a product design nature and subsequent clinical testing. The principle of steroid administration by this route is sufficiently established. Feasibility for contraception depends on a design of bracelet which will provide a sufficiently constant rate of absorption.

New intrauterine or intracervical contraceptive devices. Limited or extensive trials are in progress with at least seven new types of intrauterine devices and one that is designed to remain within the cervix. Several of these incorporate the principle of using the IUD as a carrier for an anti-fertility agent which acts locally in the uterine lumen (copper, progesterone or a nonsteroidal agent). The "copper-carrying devices" are most advanced in testing and are available generally in many countries. One of them, the Copper T, was approved in late 1974 for use in India's national family planning program. There are several versions of the Copper T under test (17, 18). The one tested longest, the TCu 200, can be left in utero for at least two years, but probably not longer than four, in order to maintain maximal effectiveness (19). This time limitation is overcome with newer models, particularly the TCu 220C, which may also have a higher contraceptive effectiveness than the TCu 200. The progesterone-releasing IUD (20), also in the form of a T-shaped plastic device, has a one-year limitation in effective time span. Present technology permits the device to release the hormone for approximately one year and this is the version which is being tested (21). Although some women have used intrauterine foreign bodies containing various nonsteroidal anti-fertility agents, this experimentation is at an early stage. Neither the form of the carrier nor the precise chemical to be used for large-scale testing has been selected.

The hope for improved performance of inert intrauterine devices currently being tested is based on design modifications, the value of which can only be determined by extensive clinical trial. One modification (the LEM) (22) is a three-dimensional form used years ago without having a distinctive performance record, but now being tested for use specifically in the postpartum or postabortum uterus. Another employs an accordion-pleated membrane designed to cover a relatively large area of the endometrium surface (23). Still another is Y-shaped (24), so as to be situated in the uterine angles and impinge upon the utero-tubal ostia. The intracervical device under limited test is supposed to influence the cervical mucus in a manner to prevent sperm penetration.

Monthly pill or suppository to be used to induce menstruation. The few compounds that have been tested as possible orally active luteolytic agents suppress the corpus luteum and bring about a menstrual discharge by eliminating the progesterone support required by the endometrium and, therefore, the initial implantation site. One of these, aminoglutethamide, does suppress corpus luteum function, but not sufficiently to bring about the desired effect (25). This particular compound is not being tested further in women as a menses-inducer, but many of its analogues are being synthesized and screened in animals for possible clinical trial.

There was some hope that a naturally occurring prostaglandin, absorbed via a vaginal suppository, could act systemically to suppress the human corpus luteum. This use of prostaglandin $F_{2\alpha}$ and E_2 has been studied without success, but there will be a continuing effort along these lines as prostaglandin analogues are synthesized (26).

Another experimental approach to menses induction in women is the use of synthetic progestins at the mid- or late-luteal phase of the cycle in order to suppress endogenous progesterone production with doses of a progestin which would not itself maintain a nascent placentation site. Four synthetic progestins were tested in women and found to cause reduction of corpus luteum function, but the effect was not sufficient to overcome the luteotrophic action of chorionic gonadotrophin (27). One compound is still being tested in this regimen.

The promise of a contraceptive method based on the principle of menses induction, whether or not a cycle has been fertile, warrants an investigative effort of the highest priority. In this approach could lie the solution to the problems of safety associated with continuous dosage forms of hormonal contraception, and a technique with near-perfect effectiveness. Not only should available compounds be tested, but special synthesis programs should be undertaken to uncover compounds that could be used in this form of contraception.

Monthly pill to cause ovulation suppression. One combination of compounds has been tested on a monthly schedule of administration for suppressing ovulation. The steroids used are absorbed from the gastrointestinal tract, stored in adipose tissue, and released gradually over a month (28, 29). The results, however, have been sufficiently disappointing that the sponsor dropped further product development. No other compound is being tested on this basis currently, but a concerted search for an anti-ovulatory compound effective as a monthly pill would have good chances of success.

Monthly pill, injection or suppository to regularize ovulation as a basis for improved "rhythm." One of the effective fertility drugs (clomiphene citrate), which acts through the hypothalamus to induce ovulation, has been tested in normally ovulating women as a means of inducing ovulation in a predictable fashion (30). The objective of this study was to improve the contraceptive use of periodic abstinence by causing a precisely-timed ovulation. This test was not successful, since with succeeding months of use the interval between drug ingestion and ovulation increased in an unpredictable fashion.

Now that a luteinizing hormone-releasing factor (LRF) has been identified, isolated, and even synthesized, the prospect of using this polypeptide for regularizing ovulation in women with normal cycles has been put to clinical test (31). The cases so far reported indicate the potential feasibility of the procedure, and the issues that need further study have been identified. These include the potential for multiple ovulations, convenient mode of administration, and consistency of response. There may now be a continuous process of synthesizing and testing of LRF analogues both for the purpose of inducing regular ovulation and with the hope of developing antagonists that would cause acceptable patterns of anovulatory cycles for contraceptive purposes. One team of investigators has identified a naturally occurring polypeptide which has the properties of an LRF antagonist.

Postcoital pill to be used regularly. Although diethylstilbestrol is now available to reduce the chances of pregnancy following isolated mid-cycle exposure (32), the accompanying side effects and disruption of the ovarian cycle make the procedure unacceptable for regular postcoital contraception. Two of the synthetic progestins have been tested experimentally as regularly used postcoital pills, but have poor effectiveness and produce considerable disruption of the bleeding pattern. One has been suggested as a possible "morning-after" pill and the other as a "minutes-after" pill (33).

Several compounds related structurally to diethylstilbestrol have postcoital anti-fertility activity in laboratory animals, and three of these (MER 25, clomiphene, and ORF 3858) have been tested without success in women (34). Others in this series are available for testing, and one is in a careful clinical trial in India (35). This type of compound has a potential for contraceptive activity that has not received adequate attention in the past.

Precoital pill to alter the cervical mucus and prevent sperm penetration. Progesterone induces thickening of the cervical mucus so that, during the normal cycle, a natural barrier to sperm penetration exists during the post-ovulatory phase (36). At least two compounds with oral activity as synthetic progestins have been tested for selective effect on the cervical mucus at doses that would not influence other progestin-responsive tissues. At first, it was believed that one of these compounds could cause thickening of the cervical mucus in the pre-ovulatory woman within two hours after taking a pill, but this proved to be an erratic response and not reliable for contraceptive purposes. At present, no compound with the unique activity desired has been identified, but various trials with the conventional progestins taken before or near the time of coitus are proceeding.

Weekly pill to disrupt endometrial development. A synthetic progestin (R2323) that can be taken weekly as an oral contraceptive is in the process of product development (37). It appears that the method will have a pregnancy rate similar to that of the now available "mini-pills" and will have a similar performance with respect to bleeding irregularities. Thus, the advantage, if any, will lie in the difference in schedule of administration.

Chemical abortifacient. The use of the naturally occurring prostaglandins or their synthetic analogues as first trimester abortifacients has been studied extensively, but the disadvantages appear to outweigh the advantages (38). Further progress will depend on the synthesis of new analogues which may be selectively more potent when acting on the myometrium than on other smooth muscle. Such studies will undoubtedly continue in the coming years, but the only immediate prospect for the application of the uterine-contracting activity of prostaglandins is in place of the use of intraamniotic saline or hysterotomy for midtrimester termination of pregnancy. No other chemical abortifacient is under overt investigation, although a natural product extracted from a Mexican plant is of current interest because of its oxytocic properties. It is believed that several of the cytotoxic agents used in cancer chemotherapy are either embryotoxic or placento-toxic when given to women early in pregnancy. On this basis, methotrexate, available for treatment of choriocarcinoma, has earned a reputation as an effective chemical abortifacient, but this use has not been subjected to controlled evaluation.

Chemical or electrocautery sterilization. Methods are now being tested, rather extensively, which cause closure of the tubal ostia by the transcervical approach. Instillation of an aqueous suspension of the well-known antimalarial, quinacrine, has been studied by several groups (39). In addition, at least one sclerosing agent has been shown to be effective in a small series of cases. Particularly for situations in which hospital bed space is limited, female sterilization as an outpatient procedure would result in greater use of this method for fertility limitation, although the irreversibility would still limit its appeal for young women of low parity. Also in an advanced stage of investigation is the use of transcervical cauterization of the tubal ostia with the aid of hysteroscopic visualization (40). This procedure is now sufficiently tested to be used by medical personnel with sufficient specialized training.

Immunization of women with an antigenic component of chorionic gonadotrophin. Although considerable basic work is still required, there has been some preliminary, limited investigation involving volunteer subjects who have received purified human chorionic gonadotrophin antigen as an inoculation designed to develop antibodies to the biologically active component of HCG (41–43). Ultimately, fragments of the molecule, readily synthesized, could be used in linkage with highly antigenic carrier molecules. Coordinate carriers could be antigens widely used in public health immunization programs (43). The purpose is to interfere with the essential, early role of HCG before a nascent pregnancy becomes established, so that the expected menstruation will take place even in a fertile cycle. A single inoculation could last more or less indefinitely but, if so, means of imparting reversibility to the procedure are essential. For example, the effect of the immunization might be overcome by the use of exogenous progestins, in order to establish a pregnancy. There are problems associated with potential cross-reaction with pituitary luteinizing hormone, partial effect, damaging the placenta, and the possibility of immunocomplex diseases that need to be resolved before unlimited clinical application is possible.

These, then, are nineteen experimental contraceptive procedures—fourteen for use by women, five by men—which have had some level of actual clinical trial by early 1975. These must be considered the major prospects for new contraceptive methodology in the near future, since they already have reached the stage of clinical investigation. Any potential method that has not yet had some degree of clinical trial is many years away from practical application, given the time needed to establish efficacy and safety.

The significance of the current items of applied contraceptive research is best put in perspective by realizing that those experimental methods which are most certain to succeed if development efforts continue are most similar to existing methods and may, therefore, have least programmatic impact. Experimental methods which are most innovative and different, having the greatest likelihood of improving upon methods currently available, are less likely to survive the critical testing phases ahead because of the uncertainties involved.

It would be foolhardy, indeed, to assume that we have now identified the ultimate objectives in contraceptive research and need only to proceed with goal-oriented work to achieve them. The continuous identification of new leads is, perhaps, the critical part of the overall process of developing new contraceptives. The development of a flow of new ideas to serve as the basis for clinical trial depends heavily on studies fundamental to a greater understanding of the normal reproductive process. Like many of the remaining problems of biomedical discovery confronting modern science, the hopes for significant revolutionary breakthrough rather than incremental advances in contraception lie in the progress of basic research.

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Discontinuation of the Pill and the IUD in the United States: 1960–1970

CHARLES F. WESTOFF, PH.D. AND ELISE F. JONES, M.A.

By 1970, nearly three of every five married women in the United States had used the oral contraceptive. Some 22.1 percent of all ever-married women were currently using the pill; 30.2 percent had used the pill for contraceptive purposes and had discontinued use; and an additional 7.0 percent had discontinued use who had taken the pill for noncontraceptive purposes (see Table I).

These data are derived from interviews with a national probability sample of 6,752 ever-married women under 45 years of age collected in the 1970 National Fertility Study, conducted from the Office of Population Research, Princeton University.* As part of a comprehensive schedule of questions on pregnancy, contraceptive and fertility histories and intentions, each woman was queried about her past and current use of the oral contraceptive, her reasons for using it (contraceptive or medical), and her reasons for discontinuation if she had stopped using it. Reasons for use and for discontinuation were elicited only for the most recent experience that had been interrupted.

Trend in Discontinuation of the Pill: Cohort Analysis

The cumulative discontinuation rate for oral contraception is shown in Table II for all women who have ever used the pill for contraceptive purposes.† These data reflect discontinuation for any reason at all; thus they reflect a mixture of the perception that contraception is no longer needed or that pregnancy is desired, as well as problems of use. The rates are shown for each cohort from 1960 61, permitting 10 years of observation up to 1970, which yields one year of observation.

The trend in dropout rates can be seen by scanning the rows across cohorts for the first several periods of experience. This shows a decline in the discontinuation rate for the first three cohorts, a leveling off through the cohort of 1965, and then a reversal. For example, the cumulative probability of discontinuing the pill in one year's time declines from .42 for the first cohort to .34 for the

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* The 1970 National Fertility Study was codirected by Norman B. Ryder and the senior author. The study has been conducted under contract with the National Institute of Child Health and Human Development, NIH, DHEW. The data were collected by the Institute for Survey Research, Temple University.

† Direct information on the purpose (contraceptive or medical) for which oral contraceptives were used, was obtained only for past users and was confined to their most recent period of use. Any previous periods of use for past users were assumed to have been for the same purpose as the most recent use. For current users, women who later reported the pill as a current method of contraception were considered to be using it for contraceptive reasons, and any past period of use for these women were also so classified.

TABLE I

Use of the Pill: 1970

Use	Percent
Total number of women	6,747*
Percent total	100.0
Now using	22.1
Discontinued use:	
Used for contraceptive reasons	30.2
Used for noncontraceptive reasons†	7.0
Never used	40.7

* Five women are excluded from this total because of no information about whether they ever used the pill.

† Includes nine women who gave no answer as to whether they were using at least partly to delay or prevent a pregnancy.

TABLE II

Cumulative Probability of Discontinuation of Oral Contraception for Any Reason by Year of Starting or Resuming Use

Cumulative Number of Months of Use	Year of Starting or Resuming Use									
	1960–61	1962	1963	1964	1965	1966	1967	1968	1969	1970
0	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
3	.22	.17	.13	.14	.11	.16	.16	.18	.18	.16
6	.36	.28	.24	.22	.22	.26	.28	.31	.29	.28
12	.42	.39	.34	.35	.35	.41	.42	.48	.47	.41
24	.58	.54	.50	.54	.50	.62	.63	.66	.65	
36	.68	.64	.64	.67	.65	.73	.76	.77		
48	.71	.68	.71	.75	.74	.82	.81			
60	.76	.72	.77	.81	.82	.87				
72	.76	.76	.81	.85	.86					
84	.80	.80	.86	.89						
96	.83	.84	.89							
108	.86	.89								
120	.90									
Number of women	156	189	291	453	593	603	648	700	700	601

cohort of 1963, remains at this level for the subsequent two cohorts, and then starting with the cohort of 1966 begins to rise until the cohorts of 1968 and 1969 (.48 and .47 respectively) and then drops with the cohort of 1970.

This is the pattern for the cohorts' first-year experience. If we focus on longer experience, the picture changes. For example, the discontinuation rate by 72 months shows an increase across the few early cohorts for which such a long period of observation is possible. This probably occurs because of events in the latter part of the decade to which we shall return shortly.

Considering the improvement in the compounds, one might have expected a reduction in the dropout rate as later users had access to better products. But since these discontinuation rates reflect so many different underlying reasons, a more refined analysis is needed to determine whether the unexpected increase in the dropout rate could be due to reasons extraneous to the use of the pill itself. About one-fifth had stopped taking the pill either because they wished to have a child or because they no longer needed contraception. These reasons are extraneous to our interest in the dropout rate resulting from various problems of use. The distribution of reasons for (most recent) discontinuation related to problems of use reported by women who had formerly used the pill for contraceptive reasons is shown in Table III. All women who reported that they had ever taken the pill but were not currently using it were asked: "Did you stop using the pill (the last time) because you *personally* had experienced physical problems with it?" A total of 70.9 percent of the women who mentioned any problem of use replied that personal physical problems had induced them to discontinue the method. This category is clearly the major source of disaffection. Women who worried about reports of danger to their health although they had not personally experienced problems of a physical nature (a category that predominates in the reasons offered by women who have never used the pill and who do not intend to use the pill in the future), comprise the second most important reason for discontinuation, accounting for 16.7 percent of the total. The remaining 12.4 percent of these dropouts are composed of women who couldn't remember to take the pill regularly or who found it inconvenient (4.3 percent), who report having become pregnant while taking it (1.3 percent), and a residual category, "other physical concerns," which includes fear of complicating existing health problems, doctor advised her to stop, and miscellaneous other reasons (6.8 percent). Differentials by age, race and religion are inconsequential, except that white women were more likely than black women to mention health worries

TABLE III

Reasons for Discontinuing the Pill the Last Time Related to Problems of Use for Women Who Had Used It for Contraceptive Purposes

Reason	Total	Age		Race		White Non-Cath.	White Cath.
		Under 30	30–44	White	Black		
Number of women	1564	896	668	1283	240	1026	257
Percent total	100	100	100	100	100	100	100
Personally experienced physical problems	70.9	69.6	72.6	70.3	77.5	69.7	72.8
Worried about reports of danger to health	16.7	17.7	15.3	17.1	12.5	17.0	17.5
Became pregnant	1.3	1.0	1.7	1.2	0.8	1.4	0.4
Other physical concerns	6.8	7.1	6.4	7.2	3.8	7.6	5.8
Problems of convenience and memory	4.3	4.6	3.9	4.2	5.4	4.4	3.5

and other physical concerns, while black women were more likely to report personal experience of physical problems.

The same kind of cohort analysis shown in Table II is presented in Table IV for women who discontinued the pill solely because of some problem in connection with use; the extraneous reasons for interrupting use in order to have a child or because of absence of need are excluded. The discontinuation rates in Table IV are therefore considerably lower than those reflecting all reasons in Table II. Moreover, since specific reasons for discontinuation were obtained only for the last time that use of the pill was interrupted, we have further confined the analysis to women who have used the pill only once, thereby excluding substantial numbers who used, interrupted use, and then resumed use of the method. The women in each cohort in Table IV, therefore, do not reappear in subsequent cohorts as many do in Table II where each use following an interruption is defined as new use.

The trend across cohorts in Table IV, however, shows a similar pattern to that observed in Table II, a decline in the 12-month dropout rate through the cohort of 1965 and then a reversal with increasing discontinuation rates for subsequent cohorts up to 1970, and an increase in the five-year or more discontinuation rate. The explanation appears to lie largely in events that began to occur in the year 1967, a conclusion that can be reached by adding the appropriate number of months required for each cohort to reach 1967 and observing the increase in the dropout rate as it is reflected in the inter-cohort comparisons. But a better way

TABLE IV

Cumulative Probability of Discontinuation Due to Problems of Use for Women Using Oral Contraception Only Once by Year of Starting Use

Cumulatve Number of Months of Use	Year of Starting Use									
	1960–61	1962	1963	1964	1965	1966	1967	1968	1969	1970
0	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
3	.14	.14	.12	.07	.06	.08	.10	.13	.12	.11
6	.23	.22	.16	.15	.14	.14	.16	.22	.23	.20
12	.25	.27	.20	.23	.19	.25	.26	.31	.35	.31
24	.30	.32	.29	.29	.26	.42	.41	.48	.53	
36	.34	.39	.36	.42	.35	.52	.57	.58		
48	.34	.42	.41	.50	.41	.62	.64			
60	.36	.44	.48	.56	.55	.70				
72	.36	.46	.52	.64	.62					
84	.41	.52	.62	.70						
96	.46	.61	.65							
108	.54	.74								
120	.56									
Number of women	63	87	133	218	273	264	298	323	324	234

TABLE V

Discontinuation Rates (percent per month) Attributable to Problems of Use for Women Using Oral Contraception One Time Only by Calendar Year of Use

Year	Discontinuation Rate	Number of Women (as of Jan. 1)
1962	2.6	53
1963	1.6	115
1964	1.5	226
1965	1.4	394
1966	1.2	571
1967	1.6	721
1968	1.8	829
1969	2.2	908
1970	2.7	921

to discuss the period effect is to examine dropout rates calculated on a calendar basis.

Period Analysis

The rates in Table V reflect the average monthly probability of discontinuation‡ for reasons of problems of use for women using the pill one time only, for calendar years covering the period 1962–1970. (The same data are presented in Figure 1 in the form of a 12-month moving average of the quarterly discontinuation rates; the moving average was adopted in order to smooth out an apparent seasonal effect in the underlying rates.) The period effect is now clear. The monthly dropout rate declined from a high of nearly three percent early in the decade to a low of nearly one percent in 1966. Thereafter the rate climbed steadily back up to its initial high in early 1970 after which some suggestion of a new decline appears. (The rates for the four quarters of 1970 are: 3.1; 2.8; 2.9; 2.0.) In order to make sure that the rise in the dropout rate in the later years of the decade was not due to a large increase in the number of new users who would make a disproportionate contribution to higher dropout rates, because of being in the first few months of use, we calculated the proportion of person-months of use contributed by the first three months for each period; it was clear that this moved in the opposite direction.

‡ Defined as:

$$q_x = \frac{b}{(a + b + c + d) - 0.5\ (c + d + e)}$$

where

a = number using in calendar month x and in $x+1$
b = number using in x who dropped out by $x+1$ because of problems of use
c = number using in x who dropped out by $x+1$ because of extraneous reasons
d = number using in x who reached interview by $x+1$
e = number beginning use in x.

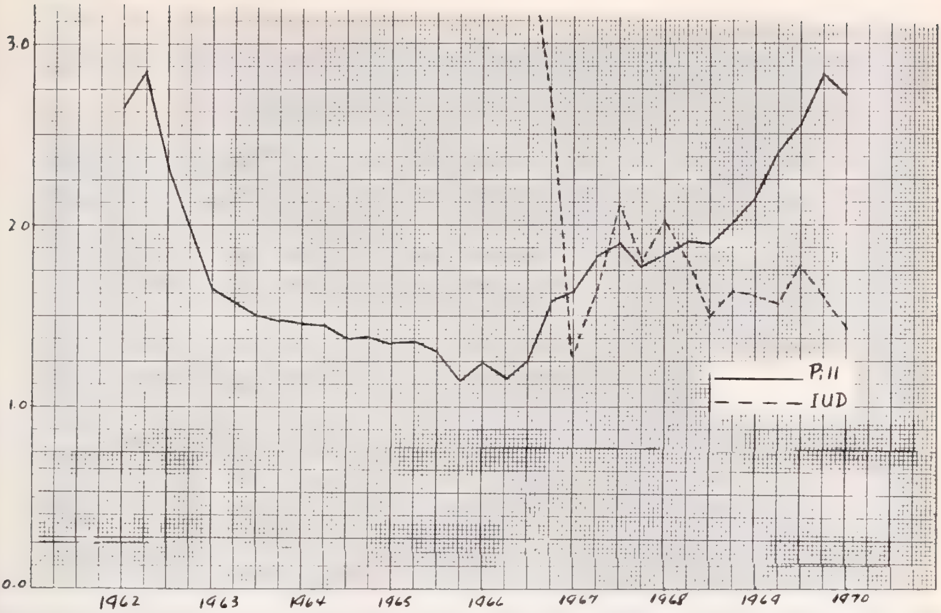


FIG. 1. Discontinuation rates (percent per month) attributable to problems of use for women who have used oral contraception or the IUD only once by calendar period of use.

The rise beginning in 1967 and continuing into 1970 corresponds with the adverse publicity accorded the pill by the disclosure of a connection between oral contraception and thromboembolic disease recorded in 1967 to 1969 in some British journals and in 1969 in studies in the United States. These were followed by the widely publicized Nelson hearings in the US Senate in early 1970 during which a great amount of critical and sometimes alarming testimony about the pill was presented. The period also saw a rash of scare books and articles in the popular press.

It seems plausible, therefore, that the sustained rise in the dropout rate that occurred in the late 1960's despite improvements in the product which reduced side effects was a result of the anxiety about serious health implications generated by responsible medical reports and sometimes exaggerated publicity. These concerns may have abated toward the later part of 1970 and it will be interesting to determine the course of the dropout rate since 1970. It should also be noted that the wide diffusion of the pill during the middle and late 1960's probably attracted many young women who were perhaps not as highly motivated as their predecessors in the earlier years and who would therefore be less likely to persist in its use in the face of critical reports.

The IUD Discontinuation Rate

A set of data similar to that for the pill was collected for the intrauterine device, but our analysis is more limited because of the shorter history and less frequent use of the method compared with the pill. In order to provide a numeri-

TABLE VI

Cumulative Probability of Discontinuation Due to the Problems of Use for Women Using the IUD Only Once, by Year of Starting Use

Cumulative Number of Months of Use	Year of Starting Use 1960–66	1967–68	1969	1970
0	.00	.00	.00	.00
3	.22	.16	.09	.10
6	.30	.20	.17	.16
12	.39	.28	.27	.20
24	.46	.32	.32	
36	.50	.39		
48	.55	.42		
60	.57			
72	.59			
Number of women	109	123	100	166

cally adequate base we have chosen to group the 1960–66 and the 1967–68 cohorts so that along with 1969 and 1970 there are only four time-period observations available. Cohort rates are presented in Table VI for women who have used the IUD one time only showing the probability of discontinuation for problems of use (this corresponds with Table IV for the pill). In the case of the IUD, unlike the pill, there is very little temporary interruption of use; the IUD tends to be used more than the pill by women who have had all the children they want. Consequently, the total number ever using the method is only slightly greater than the number having used it one time only; therefore, we have shown discontinuation rates only for the latter.

The cohort rates in Table VI show a decreasing dropout rate over time. The probability of discontinuing the method in one year's time declined from .39 for the first cohort of users (1960–66), to .28 for women starting use in 1967–68, to .27 for the 1969 cohort, and .20 for the most recent (1970) cohort. There are no exceptions to this pattern of uniform decline in Table VI and the improvement in continuation is clear. Despite this improvement, however, something approaching half of the women have discontinued the method in four years or so because of problems of use. Nevertheless, this is a better record than recent experience with the pill where discontinuation rates exceeded 50 percent after four years partly because of the anxieties discussed earlier.

The period rates of discontinuation for the IUD are shown in Figure 1 with those for the pill. Unlike the U-shaped curve for the pill, the dropout rates for the IUD (although our observation period doesn't begin until halfway through the decade) show a sharp initial decline followed after 1968 by a lower though somewhat irregular plateau.

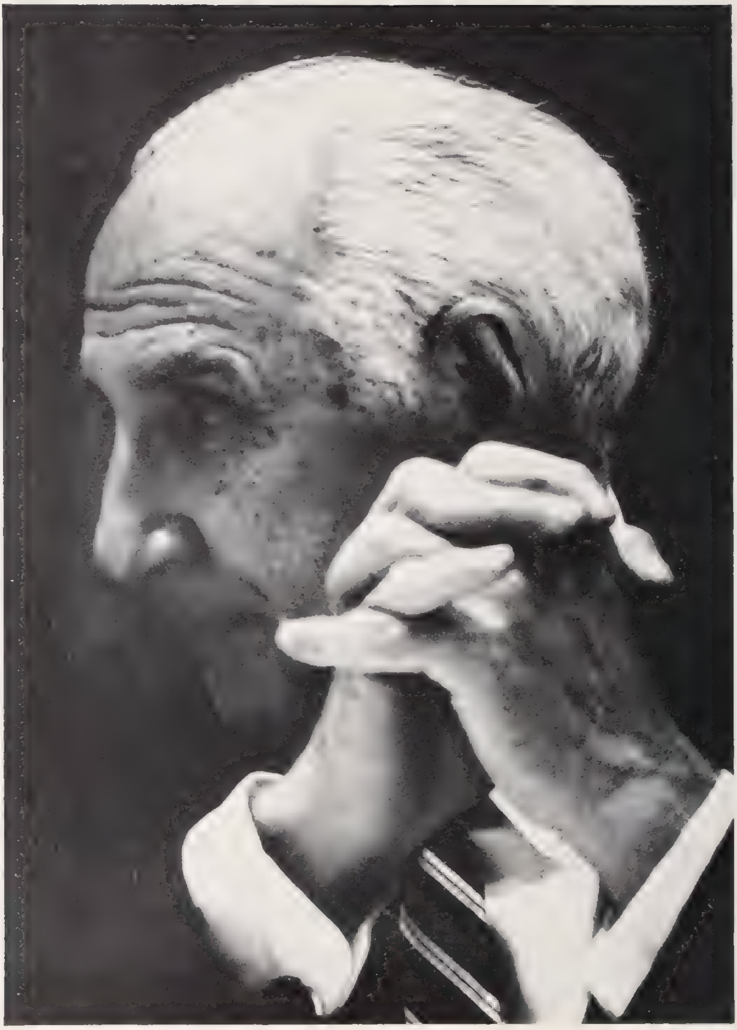
Editors' Note

During his long life (1898–1974) Alan F. Guttmacher was a practicing obstetrician, an academic teacher, a social reformer in the field of human reproduction, and a great educator whose voice was heard throughout the land and indeed throughout the world. To the authors who have contributed to this special issue of the Journal and to us, the editors, as well as to untold others, he also was a good friend and a magnificent human being.

To honor Alan's memory we have tried to bring together a series of papers representative of as many as possible of the several disciplines and areas of concern in which he was active. Since his range of interest was so broad it was difficult to organize the contributions in a meaningful way without splintering the whole into too many parts. We finally settled on four major sections: Population and Family Planning; Methods of Fertility Regulation; The Art and Science of Medicine; and Psychosocial Considerations. Within each section, papers are arranged alphabetically by first author.

Joseph J. Rovinsky
Christopher Tietze

This tribute to Dr. Guttmacher is being publihed with the support of The Guttmacher Institute, the Researh and Development Division of the Planned Parenthood Federation of America.



Advances in Understanding the Effects of Vasectomy

JOSEPH E. DAVIS, M.D. AND IRA LUBELL, M.D., M.P.H.

The increasing acceptance of vasectomy in the United States has firmly established its position as a popular option in contraceptive practice because of its safety, simplicity and relative low cost.

As of 1970, one in every six US couples having reached their desired number of children had been sterilized; and Westoff (1) has pointed out that voluntary sterilization was the first choice of couples where the wife was 30 to 44 years of age. Recent statistics reveal that this choice is not confined to the late childbearing years. Ten percent of all the sterilizations performed occurred before the wife was 25 years of age. Thirty percent occurred when the wife was 25- to 29-years-old. One-fifth of the husbands were under 30 years of age and one-half were under 35 when either they or their wives decided upon sterilization (2). According to the Association for Voluntary Sterilization, the number of voluntary sterilizations for 1974 was expected to total 1.3 million and of these, 59 percent were vasectomies.

This increased prevalence of vasectomy has brought with it concomitant changes in the religious, socioethnic, and psychosexual attitudes which have affected its acceptance.

Studies have shown that the average man choosing vasectomy in the US is white, Protestant, between 30 and 40 years of age, has been married 8–16 years and has 3–4 children (2–4). Recent findings, however, indicate a greater number of Catholics opting for vasectomy. In one study, of the 189 men that were vasectomized, almost one-half of those with known religious preference were Catholic, one-third were Protestant, and one-fifth were Jewish (5).

Since the Roman Catholic Church condones only the rhythm method of contraception, the relatively high percentage of Catholics opting for vasectomy might be an indication that an individual's choice of method might be less dictated by his religious affiliation than by his needs.

Different studies also indicate different educational and socioeconomic levels of vasectomized men in this country. Generally, findings indicate that men choosing vasectomy have higher incomes and more schooling than the general population. Minority groups, especially blacks, have consistently been underrepresented (1, 2, 6). The reasons elicited for this phenomena include the fear of genocide, masculine gender role, the ability to father children as a sign of masculinity, and the fear of surgery. In a recent study, 498 black couples in the USA were

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interviewed on their attitudes toward sterilization. Over 50 percent of those surveyed believed sterilization was a method of genocide and 84 percent of the men interviewed rejected sterilization (7). With time and a more concerted research effort on the motivation and acceptance of vasectomy in minority groups this social phenomenon might change.

Regional differences seem to exert an effect on the popularity of vasectomy in a given area. One study based upon the data from the 1970 National Fertility Study demonstrated that 11% of all married couples, with husband present and wife under 45 years of age, had undergone contraceptive sterilization. This 11% represented a little over 2.75 million US couples and 5.1% of these sterilizations were vasectomies. The lowest rate of vasectomies was in the mid-Atlantic states (1.5%) compared to 12.0% in the Pacific states. The highest proportion of men sterilized among low-income couples was found in the West (6.9%) and the lowest rate in the South (1%), with 2.6% being the national low-income average (13).

In the realm of the psychosexual attitudes following vasectomy, recent American studies have confirmed previous findings of greater sexual pleasure post-vasectomy. Freund and Davis (9) reported increased sexual desire and satisfaction with greater coital frequency among vasectomized men. Uehling and Wear (10) and Nash and Rich (11) also noted similar findings. Generally, studies utilizing questionnaires, interviews and psychological tests on the after-effects of vasectomy are in agreement in their findings expressing satisfaction with the procedure on the part of both husband and wife. These studies also, for the most part, reported "improvement" or "no change" in sexual satisfaction, marital harmony and general health. To date, studies done in the US have shown that the decline in sexual desire or frequency tends to fall below 5 percent with aging and other (nonvasectomy-related) factors influencing the percentages.

To date even with its increased popularity and acceptance, the American public's attitude towards vasectomy is a mixture of skepticism and ignorance. Negative attitudes were firmly demonstrated in a study conducted by Rodgers et al (12). Subjects were asked to rate a hypothetical middle class American couple utilizing an adjective check list and a person description scale. Some raters were told the couple had a vasectomy while other raters were told the couple were using ovulation suppressants. All other descriptions of the couple remained the same. The couple using the pill obtained significantly more favorable description ratings than the vasectomy couple. Vasectomy seems to connote castration among segments of the population (2). Misinformation prevails even in intellectually sophisticated environments. A study conducted at a leading university demonstrated that misinformation and prejudice against sterilization were prevalent among the student body and even the biology faculty, in which 14 percent of the respondents believed that vasectomy curtailed a man's ability to ejaculate. Others believed effects resulting from vasectomy included loss of virility, loss in the ability to achieve orgasm, and even a change in voice pitch (13).

These findings clearly indicate a need for increased educational programs in voluntary sterilization in the context of a method of family planning. The dissemination of information about surgical contraception will help in the better understanding of vasectomy—its purpose and its after-effects—and will help eliminate the adverse myths, fears and misconceptions.

Interest in vasectomy—a permanent, though not necessarily irreversible form of surgical male contraception—has also stimulated research into the effects of surgical vasocclusion, foreshadowing advances in our understanding of the normal reproductive tract and male infertility.

The development of better techniques for the performance of vasectomy undoubtedly will enhance the chances for successful functional reversibility (i.e., a fertile state postvasovasostomy).

Research into vasectomy and its sequelae and effects has resulted in better understanding of the mechanism of sperm transport during ejaculation. Formerly, urologists had advised a period of from six weeks to several months of contraception following bilateral vasectomy or until two semen specimens without sperm had been produced. In a study performed by Freund and Davis (14) to determine the exact end point in terms of the number of ejaculations postvasectomy required to render a patient's semen aspermic, it was apparent from the data, in which preoperative and consecutive postoperative semen specimens were studied, that approximately 60 to 70 percent of the sperm in the normal ejaculate from an intact (i.e., unoperated) man come from that part of the vasa proximal to the point of vasectomy and from the epididymis, since the first specimen after vasectomy consistently contained about 30 to 40 percent of sperm found in the preoperative specimen. The constant percentage decrease in sperm output with successive specimens after vasectomy suggested that ejaculation is a true biologic emptying phenomenon and that at ejaculation approximately 65 percent of the sperm distal to the point of vasectomy are expelled from the vasa. In over 100 patients studied, absence of sperm was noted after six to ten ejaculations following vasectomy. By virtue of this technique, the urologist and patient, with the cooperation of the laboratory performing the sperm counts, can determine within a relatively short period of time after the operation that aspermia has been produced and that the procedure has been successful.

The low functional success rate of vasovasostomy is not understood because it occurs despite the fact that the surgeon can routinely produce a successful anatomical vasovasostomy. The lack of data on the physiologic mechanisms regulating sperm transport in the male reproductive tract made it advisable to study the contractility of the vas deferens in vitro (15). Vasa obtained from cadavers and from vasectomies under general, spinal, and local anesthesia were used. The spontaneous motility and response to norepinephrine of the human vas was studied. The studies indicated that the human vas deferens has spontaneous motility in vitro without nerve stimulation. It is not inferred that nerve stimulation plays no role in regulating the motility of the vas, but rather suggests that the results obtained by others on the isolated guinea pig vas deferens, in which no spontaneous motility was observed unless there was nerve stimulation, must be carefully reexamined. There was a marked difference in motility patterns between vas segments obtained from vasectomies under general anesthesia and from cadavers on the one-hand and from vasectomies under spinal anesthesia on the other hand. It was felt that the intrinsic rhythmicity of the human vas depended upon the local concentration of norepinephrine, while the powerful and coordinated series of contractions that propelled the sperm from the epididymis to the urethra during ejaculation are initiated and controlled by the release of substantial amounts of norepinephrine from the sympathetic nerve endings. If it follows that sperm pass from the epididymis through the vas during the series of coordinated contractions of the vas deferens (and this coincides with the original study indicating that approximately 60 to 70 percent of the sperm in a normal ejaculate from an intact man comes from the part of the vas proximal to the point of vasectomy), then it follows that a powerful series of coordinated contractions of the vas deferens is required to transport large numbers of sperm from the epididymis and the proximal vas along the length of the vas to the urethra during seminal emission and ejaculation. Vasectomy, however, normally results in a division of the sympathetic nerves to the vas as well as removal of a relatively large segment of the vas. An intact sympathetic nerve supply may be vital to the transport of sperm from the epididymis at the time of ejaculation. Increasingly, urologists are advising that a small or no segment of the vas be removed, but that the ends be separated by fascia and the proximal end of the vas be fulgurated so as to preserve as much of the vas as possible and make reanastomosis more feasible functionally.

Vasectomy has provided a means for separating the sperm and semen fractions of the ejaculate. As yet, there is no reliable simple method for assessing the functional status of the epididymis in infertile men. If a component of semen is found to be specific or nearly specific to the epididymal secretion, and if it is present in high enough concentration in semen to permit assay, a chemical assessment of epididymal function would be possible. Glycerylphosphorylcholine (GPC) appears to be a semen component that meets these criteria. Experiments in our laboratory (16) indicate that about three-quarters of the total GPC content in human semen is contributed by the epididymal secretion. The concentrations of GPC and carnitine compounds (ordinarily present in high concentration in the mammalian epididymis) were determined in normal human semen and in semen obtained after vasectomy. Concentrations of GPC were markedly lower in vasectomized semen. It is estimated that approximately 70 percent of the GPC present in human semen is derived from the epididymal secretion. It may be possible to estimate GPC levels in semen as a measure of epididymal function.

In men undergoing vasovasostomy, it has become possible to do ultrastructural studies of the testis and to study the long-term effects of vasocclusion upon human spermatogenesis (17). To study the morphologic effects of vasectomy, testicular biopsy specimens from three to seven years postvasectomy were fixed, embedded, and stained for light and electronmicroscopic examination. Sections of the seminiferous tubules showed: 1) The blood supply to the tubules was intact. 2) The lumen of each tubule examined was patent. 3) The Sertoli cells appeared to be intact, with elongated cell outlines, radially oriented, dense cytoplasm, prominent endoplasmic reticulum, lipid droplets, subsurface cisternae adjacent to Sertoli cell junction, and nuclei with characteristic clefts and large tripartite nucleolus. However, a large number of lysosomes were present in the area between nucleus and basement membrane as intact dense bodies and as membrane coated electron-lucent formations. 4) The germinal epithelium was present and showed normal stages of spermatogenesis, suggesting that vasectomy does not inhibit sperm formation. Spermatids were seen in the usual clusters of four to five. However, spermatozoa were not observed in their typical location close to the lumen, enwrapt by digitations of Sertoli cells, but rather appeared abutting the basal portion of Sertoli cells, often close to the basement membrane of the tubules. This peculiar location might indicate that these Sertoli cells were acting to absorb or eliminate the sperm. These ultrastructural findings suggest that the human testicle may actually deal with the sperm which are not ejaculated and which do not pass through the vas deferens. This would be a deviation from the current concept of sperm absorption which suggests that this occurs in the epididymis. These studies are in progress and will be complemented by studies of a prospective nature in animals to determine ultrastructural and histochemical effects of vasectomy.

The question of immunologic consequences following vasectomy are of great interest today (17). No systemic diseases of an immunologic nature have been proven to be due to vasectomy, but Shulman and Davis (18) and Ansbacher (19) have shown that in over 50 percent of men in the first year following vasectomy, there are factors in the serum which will cause agglutination of donor sperm. Normally, spermatozoa are sequestered behind a barrier limiting both their potential to immunize the male and their vulnerability to immune damage. Disturbances of this barrier might occur after vasectomy when massive sperm absorption may take place somewhere in the genital tract, or as a result of testicular biopsy through a transient release of an immunizing dose of spermatozoa. This immunity usually is not a high titer response and may decline with time. The immunity following vasectomy or biopsy need not be deleterious. When the testis barrier is breached, however, a further possibility arises, namely, autoallergic orchitis. Clinically, the incidence of orchitis following vasectomy is extremely low. Ansbacher (18) has shown that the titers of humoral antibodies decrease two to three years following vasectomy. The mechanism of the humoral response is not yet known. It should be noted that the standard Kibrick test measures only IgG, while the sperm immobilization test measures both IgG and IgA. The origin of the immune response that may take place after vasectomy in man has not been demonstrated. Although antibodies have been reported in the blood of a certain percentage of men after vasectomy, the antigenic stimulus for antibody production has not been localized. Since the presence of such antibodies in only about one-half the vasectomy patients can be demonstrated, it is difficult to propose a unifying hypothesis. If the immune response is a classic pathophysiologic response in the epididymis to the presence of excess numbers of sperm that takes place weeks, or even months, after vasectomy, it should occur in all immunologically competent men. The verification of such a classic immune response requires the experimental demonstration of the steps involved, including the primary reticuloendothelial system response, the presence of 19S-containing lymphocytes, the secondary response in the epididymis which involves macrophage activation with the stimulation of the large lymphocytes to produce the characteristic small lymphocytes, and the migration of the small lymphocytes to the testis. The experimental verification of such an immune response has not as yet been provided, and the need for such research work is urgent.

It is also necessary to characterize the specific immunoglobulins involved in the immune response. The basic research on immunology should have a high priority since it is essential to understand the underlying phenomena involved in view of the anecdotal, unsubstantiated, and damaging reports in the lay press on the long term sequelae of vasectomy that are attributed to the immune response.

Five areas of biomedical research have been investigated as a result of the growing interest in vasectomy. Hopefully, these areas of investigation will lead to a better understanding of the effects of vasectomy and will provide a basis for better understanding of male reproduction and infertility.

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Diabetes Mellitus in Pregnancy

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Many excellent summaries of the literature have been presented in the last several years concerning pregnancy complicated by diabetes mellitus (1 16). This condition is becoming one of the major complications of obstetrics. Better medical control means that increasing numbers of diabetics are able to reproduce who previously were not. The pregnant diabetic and her fetus and newborn are confronted with numerous problems. The pregnancy affects the diabetes and the diabetes affects the pregnancy.

In the less severe forms of diabetes, particularly when the diabetic is not well controlled, infants tend to be large. When maternal vascular disease is present, intrauterine growth may be retarded. Perinatal mortality in the insulin-dependent diabetic ranges between 5 40 percent, depending on the severity of the disease and the quality of the care rendered. The infant, regardless of gestational age, is more likely to suffer from hypoglycemia and respiratory distress, particularly when the mother has not been rendered proper care. The incidence of congenital anomalies in the newborn is said to be 2-4 times the expected rate. The incidence of toxemia of pregnancy is estimated to be greater in patients who do not receive proper diabetic control. Hydramnios is a complication frequently encountered.

Carbohydrate tolerance and insulin requirements frequently change throughout pregnancy. The majority (70–80 percent) of diabetics will have an increasing insulin requirement during pregnancy, necessitating close observation and care. It must be emphasized that the best obstetric results are obtained in patients in whom euglycemia is maintained. Urinary tract infections in diabetics can be frequent. Whether pregnancy hastens vascular complications has not been definitely established. It must be emphasized to the patient that even with optimal care she cannot be assured that her child will be born healthy and alive. However, investigators must be careful not to dilute their series with Class A diabetics, as they are a different type of patient from the insulin-dependent diabetic. Individualized attention by a skilled team of physicians yields the best results in these complex pregnancies.

Diagnosis

Few problems exist in diagnosing the overt diabetic. However, there is considerable controversy concerning the so-called "Class A," or gestational diabetic. The definition as well as the method of diagnosis vary from group to group. In general, if the 3-hour glucose tolerance test is abnormal, the patient should be treated as a diabetic.

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There are many reports concerning the diagnosis of abnormal carbohydrate metabolism during pregnancy. It has been established that there is a 25% increase in renal blood flow during gestation and a 50% increase in glomerular filtration (7). More glucose molecules therefore are presented to the renal tubules for reabsorption even at a constant blood glucose level. Therefore, glycosuria can occur during pregnancy with essentially normal blood sugar levels. The patient with diabetes best can be diagnosed by means of blood glucose levels. Carrington advocated that every pregnant woman should have a 2-hour postprandial blood sugar sometime during her pregnancy (1). This would be a required part of the prenatal evaluation, just as are serology or hemoglobin determinations. Attention also should be focused on patients who have a family history of diabetes; who have given birth to infants weighing more than 9 lbs; who previously have delivered children with congenital anomalies; or who have a history of previous unexplained stillbirth.

Problems arise when attempting to diagnose the Class A or gestational diabetic. The oral glucose tolerance test is altered during normal pregnancy. O'Sullivan and Mahan (8) developed criteria for the interpretation of this test in pregnancy. Their maximum allowable values for blood glucose include a fasting value of 90 mg%. Burt (9) attributes the lag type oral curve in pregnancy to delayed gastrointestinal absorption. Because of variables in the oral glucose tolerance test during pregnancy, some investigators have advocated the intravenous glucose tolerance test, which eliminates absorption factors (10). A typical procedure is to give 25 gms of glucose intravenously as a 50% solution, and then measure blood glucose levels at frequent intervals. By following the blood glucose during the first hour after injection, the time required for one half of the administered dose to disappear can be calculated. An expression of glucose tolerance can then be derived in terms of mg of glucose metabolized per minute (11).

Conflicting results between the oral and the intravenous glucose tolerance tests in the same individual have occurred. Ocampo and associates (12) found normal intravenous tests in 22 subjects who had abnormal oral results. Benjamin and Casper (13) report considerable experience with both tests during pregnancy. They demonstrated that although the false positive rate is slightly higher for the oral test, 10.6%, than for the intravenous test, 4.3%, in pregnancy the false negative rate is considerably higher for the intravenous test (47%), than for the oral test (12%). Baker and coworkers (14) agree, but they feel that the fetal outcome is more accurately predicted by the intravenous test.

The frequency of the diagnosis of gestational diabetes is proportional to the diligence with which one seeks the disease. An increased perinatal mortality has been demonstrated in pregnancies in which an abnormal glucose tolerance pattern is found. Grimaldi found an identical perinatal mortality in highly suspect patients whether the glucose curve was normal or abnormal (15). Dandrow and O'Sullivan (16) did not change the perinatal mortality or incidence of congenital anomalies in infants born of patients with abnormal glucose curves when a standard small dose of insulin was administered. The importance of finding gestational diabetes is indicated by the study of O'Sullivan (17) who found that

$5\frac{1}{2}$ years after abnormal tests during pregnancy, 28.5% of the woman had overt diabetes. Mickal and associates (18) found the incidence to be 60% after 12 years. All pregnant women at high risk for diabetes, including those with glucosuria, should have a blood glucose test during pregnancy. The oral test seems to be more sensitive, but the intravenous test is easier to interpret and may reflect the fetal outcome as well, if not better, than the oral test. Unfortunately, fetal problems seem to occur even if the abnormal blood glucose patterns are treated.

Management of the Pregnant Diabetic

Perinatal mortality is lower in the pregnant diabetic in institutions that utilize the combined efforts of the internist, obstetrician, and pediatrician (1-6). Experienced physicians can achieve a perinatal mortality rate as low as 5%–12%. The obstetrician and the internist should see the patient at least every two weeks during early pregnancy and after the 30th week at least weekly. Normoglycemia with avoidance of acetonuria and treatment of early problems such as fluid retention, hypertension, retinopathy, and albuminuria are essential.

As soon as pregnancy is established, a complete evaluation of the diabetic patient should be undertaken. This evaluation includes the usual physical examination, including a careful search for evidence of vascular disease. Laboratory studies include a search for albuminuria, abnormalities in the urinary sediment, blood glucose levels, blood urea nitrogen, and possibly x-ray studies of the lower extremities to detect vascular calcifications.

The patient must understand the necessity for a carefully supervised pregnancy. It is essential to educate her as to the economic aspects of intensive medical care. She should be informed that there is likely to be an early termination of pregnancy and that the possibility of cesarean section is present. Careful adherence to the prescribed routine is important, but no guarantee of a healthy infant can be given.

The pregnant diabetic of normal weight may be permitted to gain 15–25 pounds. The obese patient will require fewer calories, and should be restricted to 1500 calories per day. Total calorie intake may range from 1500 to 3000 calories per day, calculated on the basis of ideal weight. Generally, 100–200 calories per day are added to meet the requirements of pregnancy. One and a half to 2.0 gm of protein per kilogram per day are optimal (4).

The insulin requirement during pregnancy frequently is increased progressively with the duration of pregnancy. It has been emphasized by many that successful outcome of pregnancy is more closely related to the quality of metabolic control than to any other feature of management (5). This requires strict control of blood sugar at or near normal levels throughout gestation. Glycosuria may have to be tolerated in pregnancy so long as carbohydrate utilization is adequate and blood sugar levels remain within the acceptable limits of below 120 mg% two hours postprandial. Glycosuria in the presence of acceptable blood sugars may occur, and one must perform quantitative 24-hour urine glucose levels to determine how much carbohydrate is lost. If there is more than 20 gm of glucose in a 24-hr urine collection in the absence of hyperglycemia, the diet should be supplemented by the amount of carbohydrate that the patient is losing (4). Many authors have stressed the necessity for maintaining normal blood sugars and preventing ketonuria (4, 19). In a study by Churchill et al (19) in which a prospective assessment of diabetic pregnancies and their children was carried out, complications of diabetes such as severity (White's Classification), acetonuria, insulin reactions, and prematurity were evaluated. Subjects were matched with nondiabetic controls. It was found that the diabetic mothers with acetonuria had offspring with a lower I.Q. than control patients. This was statistically significant. The offspring of diabetic patients without acetonuria had I.Q.'s equal to those of controls. This association between maternal diabetes complicated by acetonuria and I.Q. of the children was present in mild as well as in severe diabetes, including gestational diabetes. No significant effect of insulin reaction in the mother on I.Q. of the offspring could be demonstrated. The association of diabetes with acetonuria in respect to I.Q. of offspring was independent of the duration of the pregnancy. Caldwell and Churchill (20) have shown that the quality of the food the fetus ingested influences cerebral development. Restriction of protein during pregnancy in rats results in small offspring with decreased learning abilities.

The hormonal treatment of diabetes in pregnancy has had a stormy career. It has been abandoned because of the premalignant and malignant lesions in the female progeny of women who received nonsteroidal estrogens during pregnancy. However, hormonal therapy in general has not improved fetal salvage.

Controversy has arisen over the use of pregnanediol determinations during gestation and their accuracy in depicting the vitality of the fetal-maternal placental complex (4). Early reports looked encouraging. It is now generally conceded that this determination is not of great value either to manage the pregnancy or to determine time for delivery. Urinary estriol determinations have been shown by most investigators to be a helpful index of the intrauterine environment (22, 23, 29). However, there are some who have not found this to be true in the diabetic (25).

Timing of Delivery

The insulin-dependent diabetic is usually delivered between the 34th to the 38th week of gestation. The more severe the diabetes, the earlier the date usually chosen for delivery. Complications such as preeclampsia, repeated ketoacidosis, marked hydramnios, a previous history of fetal death in utero, advancing retinopathy, preexisting renal disease with hypertension and albuminuria early in pregnancy, and/or progressive renal failure may demand delivery at the 34th or 35th week of gestation. Toxemia is generally accepted as an indication for prompt delivery when it occurs. Most clinicians accept the concept that the hazard of intrauterine death in the preeclamptic maternal milieu is much greater than the risk of neonatal death. A decrease in insulin requirement, decrease in fetal movements, or change in fetal heart rate are indicators of fetal distress.

Lecithin/Sphyngomyelin (L/S) ratios have been helpful in timing delivery for those patients. Generally they should have a ratio of 3:1 before undertaking delivery (27). Another valuable test is the oxytocin challenge test in which fetal distress is an indication for delivery. If the oxytocin challenge test is normal, it has been documented that fetal death usually will not occur within a week (28).

Urinary estriol studies can be of great help after the 34th week of gestation (22). It has been our policy that if the urinary estriol is normal in insulin-dependent diabetics, we carry the patient to 36 or 38 weeks depending upon the patient's general condition. However if the urinary estriol falls to a lethal level, below 4 mgs, after the 34th week of gestation and other factors indicate that the fetus is able to survive, prompt termination of pregnancy is indicated. If urinary estriol stays in the normal range, pregnancy is usually terminated at 36 and a half to 38 weeks. Control of blood sugar is essential, as well as avoiding acidosis. Since it has been shown that episodes of ketonuria are deleterious, we prefer to deliver as soon as the fetus is mature (as indicated by the L/S ratio) or the estriol level is so low that fetal death may ensue.

A problem frequently occurs as to gestational age, since often the patient does not know exactly when she conceived and/or the fetal size does not appear to be consistent with dates. Other tests must be employed, such as x-ray of the fetus for femoral epiphyses and amniotic fluid creatinine determination. Maternal estriol excretion can be a useful tool when used as part of the clinical management. Estriol in the insulin-dependent diabetic can be consistently subnormal. The obstetrician is then faced with a dilemma, for such subnormal estriol excretion may indicate a stunted fetus or congenital anomalies. In the absence of other indications for delivery, the patient is allowed to continue the pregnancy in hopes of achieving more normal values.

Cesarean section is becoming perhaps the major method of delivery. Since the cervix at 37 to 38 weeks of gestation is frequently not conducive to an easy vaginal delivery, many feel that it is not fair to subject the fetus to the stress of labor under such circumstances in a pregnancy in which one has invested great time and effort. However, with sophisticated monitoring devices now available, we have means of detecting fetal distress during labor (24). With the combination of maternal estriol determination and fetal monitoring during labor, vaginal delivery might be accomplished more frequently. However, in clinics which do not have this capability, it may be advisable to deliver the patient by cesarean section, unless easy vaginal delivery can be accomplished. The great majority of Class A diabetics should be delivered vaginally at term, providing all indices are normal.

Hospitalization is mandatory when complications arise. It has been shown that clinics which demonstrate the best perinatal mortality are those that hospitalize their patients early in gestation at 28 30 weeks (5). These clinics routinely admit their patients from the 30th to the 34th week gestation for meticulous control of blood sugars during these very critical periods. This may be an economic problem, but the results are fine.

Following delivery, there is an abrupt fall in insulin requirement. Therefore, in the patient undergoing induction of labor or cesarean section it is essential not to give long-acting insulins. They should be managed by intermittent doses of crystalline insulin and the patient supplemented with adequate amounts of intravenous glucose.

The Role of Therapeutic Abortion and Future Pregnancies

It is the feeling of many that Class F diabetics should not attempt a pregnancy and that therapeutic abortion is indicated (4, 5). Progressive renal failure, coronary artery disease, pelvic iliac artery disease, and advancing retinopathy are nearly absolute indications for interruption (4). Pregnancy is unwise in the presence of such complications. However, in cases of mild retinal or renal changes, it is often impossible to deny a woman a trial of pregnancy when she is willing to assume the risks, costs, and disappointments of fetal or neonatal loss.

Many advise that the insulin-dependent diabetic limit her reproductive career to two or three viable pregnancies. The severe diabetic will be fortunate if she can complete two successful pregnancies. Consideration should be given to the likelihood of the progeny being diabetic (26). This risk increases greatly when both parents are diabetic.

In summary, diabetes is a disease complicating pregnancy that carries hazards both for mother and fetus. Meticulous care by a group of internists, obstetricians and pediatricians interested in this problem can produce optimal results. Our knowledge has increased greatly, with the use of modern clinical laboratory tests being developed. Perhaps the perinatal survival will be further increased. The outlook for long-term reproductive efficacy is guarded when one considers what effect this metabolic disease has on pregnancy.

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Immunochemistry of a Reproductive Antigen Involved in Sterility and Fertility*

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Introduction

This report focuses on a field that was of continuing interest to Dr. Guttmacher for more than 30 years since he was coauthor of a paper entitled "Experimental Observations on Sperm Immunity in the Rat" (1). Although the "slight reduction in fertility" was considered insufficient for "practical importance," Dr. Guttmacher never lost his enthusiasm for the objective, and continued to encourage others in this field. Having had the benefit of his direct, friendly, and active encouragement for so many years, we take great pleasure in demonstrating how prescient Dr. Guttmacher was.

The state of the art in immunoreproduction (a term introduced to identify this specialty) (2) has been summarized in several reviews (3-6). The following points are clear: 1) There is a large body of literature supporting the thesis that immunologic approaches can induce infertility in experimental animals; and 2) there is a growing awareness that infertility caused by immune responses may occur spontaneously in human males and females. However, unequivocal evidence establishing the link between immune reactions and infertility in humans is yet to be acquired. This lack of certainty can be attributed to the lack of definition of antigen-antibody system(s) involved. To resolve the uncertainty, it is required that all antigen-antibody systems participating in reproductive failure be fully defined. Until even one such antigen has been identified chemically and immunologically, the entire field of immunoreproduction will continue to languish in speculative limbo. For example, even the attribution of sperm agglutination as a causal factor in sterility based upon immune mechanisms cannot be accepted until the appropriate antigen-antibody system has been elucidated and the correlation between antibody titer and effect is established. Accordingly, we have devoted our efforts and resources towards these goals.

EXPERIMENTAL

Aspermatogenic Antigen (ASA)

In addressing the problem of characterizing a reproductive antigen, election of the appropriate starting point is critical. The syndrome of immunologically

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induced aspermatogenesis in the guinea pig was selected as a laboratory model. If significant progress could be made in isolating and characterizing this antigen, great stimulus would be imported to the field. Moreover, accounting for at least one antigen would permit attack on other antigenic substances, of which there may be some five to seven from sperm alone (e.g., head antigens, tail antigens, proteinases, hyaluronidase). The aspermatogenic syndrome had been described and initial attempts made to extract the active antigen (7, 8). Notation of polypeptide and polysaccharide moieties was made (9) and extraction using phenol and papain was reported (10). The amino acid content of guinea pig and human antigenic material was described (11). Inactivation of the antigen by enzymes and by tissues and sera was demonstrated (12) and it was recorded that pepsin could be employed as a first important step in the purification of the antigen (6). Voisin and Toullet (13) claimed the separation of four antigens from sperm, two of which appeared to be involved in aspermatogenesis. Further progress in purification of ASA was disclosed recently (14).

Two procedures were used for extraction of ASA. In the acetic acid methods, fresh or frozen-thawed testes, epididymides, or sperm (flushed from epididymides) were homogenized (1 min, Waring blender, high speed) in an equal volume of 0.1 M acetic acid, stirred at 4°C, and centrifuged (8,000 × g, 20 min.), after which the supernatant fraction was treated with 30% trichloroacetic acid to make a final concentration of 5%. This material was centrifuged, dialyzed overnight, extracted with butanol-chloroform, and the resultant aqueous solution was lyophilized. For Sephadex fractionation, 100 mg was dissolved in 2 ml 0.09 M acetic acid, pH 3.0, and loaded onto a Sephadex G-50 (fine) column (1.5 × 85 cm). The sample was washed on with 1 ml acetic acid and eluted with 0.09 M acetic acid; 2 ml fractions were collected at a flow rate of 10–12 ml/hr. The column effluents were monitored by absorption at 280 mu (model UV 280 IF recording ultraviolet absorption meter) and collected with a Gibson Model LB-1 fractionator. The resulting 5 fractions were lyophilized and tested for antigenic activity by bioassay and by PHA (passive hemagglutination) inhibition (14). The most active moiety then was reacted with antibody.

Antibody

Sera obtained from guinea pigs rendered aspermatogenic were titered (PHA) and if the titers exceeded 100,000, they were mixed with an equal volume of a saturated ammonium sulfate solution and the precipitate was redissolved. This procedure was repeated three times, after which the material was dialyzed, adjusted to pH 5.9, and centrifuged. The supernatant corresponds to the pseudoglobulin fraction of serum. A known amount of the antibody preparation was dissolved, titered, and mixed with a known weight of active antigenic fraction (which was also titered). After several runs, the antigen-antibody complexes were dissociated and the resultant materials were loaded on a Sephadex G-75 column: The antibody was recovered as a sharp peak in the void volume, while the antigen was eluted as a peak in the bed volume. The antigen was recaptured and used for molecular weight determinations, for acrylamide gel electrophoresis, for immunoelectrophoresis, and for chemical analyses.

In the concanavalin procedure, Con-A-Sepharose (Pharmacia) was used for affinity chromatography in a temperature-controlled water-jacketed column. The sample was dissolved in appropriate buffer and washed onto the column. After the first 20 ml, fraction I was collected in the next 20 ml and after 20 ml of buffer, alpha methylglucose was added to appropriate concentration, displacing the absorbed material. The next 40-70 ml was collected as fraction II (the absorbed material) and after 30 ml of buffer containing the alpha methylglucoside had entered the column, the column was washed with 50 ml original buffer. (Details on this and the molecular fractionation procedure will be published elsewhere.)

RESULTS

Antigen

In the acetic acid method, a single sharp peak (PHA-tested) was obtained. After complexing with antibody and subsequent dissociation, the antigen gave a single band in acrylamide gel electrophoresis. In immunoelectrophoresis, the material moved toward the cathode and gave a single precipitin band. In calibrated Sephadex G-50 columns, the antigen could be assigned a molecular weight of 12,600. Amino acid, carbohydrate, and linkage analyses permit the deduction that the antigen is a glycopeptide containing approximately 13% carbohydrate (galactose, mannose and N-acetylglucosamine) with the galactose residues at the nonreducing end of the polysaccharide. The polysaccharide appears to be attached to a polypeptide of 100 residues through an N-glycosidic linkage.

From the concanavalin studies, it was determined that a product can be obtained which is equivalent to that following pepsin digestion (a significant advance which, at the least, obviates the possibility of transpeptidization). Also, essentially all ASA was recoverable in a single peak (Fraction I). Upon electrofocusing, the purity of this product was readily demonstrable, since only one fraction (250 μm) was active biologically and the purity was further verified in the fluram assay (15). Further, purity was ascertained by immonodiffusion studies in which only one precipitin band was obtained.

Antibody

Since it was essential for studies on identification and purification of antigens that the respective antibodies be isolated and identified, such experiments have gone on simultaneously. Certain of these studies describing identification of antibodies and correlating the antibody titers with infertility in male and female experimental animals have appeared elsewhere (17, 18). It is pertinent to note that antibody to ASA is identified with the pseudoglobulin fraction, and that rabbit anti-guinea pig IgG can precipitate the soluble antigen antibody complex

(ASA). Thus, having previously labeled the antigen with fluram, a simple, rapid assay is available for the antigen and antibody.

These studies have been extended to humans. Human testicular extracts have been made, labeled with fluram, and reacted with globulins from infertile and fertile couples. It has been found that a small number of patients with idiopathic infertility exhibit strong positive responses using this test. The nature and extent of these reactions have yet to be evaluated fully because these studies have only recently been performed. It seems clear, however, that the laboratory models hold great promise for the studies on humans.

Discussion and Summary

These studies demonstrate clearly the feasibility of isolating, extracting, and purifying the antigen involved in aspermatogenesis. Also, since the corollary studies depended upon isolation and identification of the respective antibodies, it is equally clear that the feasibility of isolating and characterizing the respective antibody has been demonstrated. Using these studies as prototypes, it now becomes possible to apply this knowledge to similar studies on other reproductive antigens of experimental animals and to humans as well.

With respect to similar studies on other reproductive antigens, progress already is being made on the hyaluronidase antigen-antibody system (16). Also, it should now be possible to separate and identify agglutinating and immobilizing antigen-antibody systems. Further, we plan to isolate head and tail agglutinating antigens.

With respect to the human studies, the preliminary findings indicate that attribution of antibody response in certain cases of infertility may be placed on firmer footing. Moreover, these studies offer the hope of correlating infertile conditions with levels of antigen-antibody interaction. Conceivably, the hope of Dr. Guttmacher for an immunologic method for fertility control can be obtained and the correction of existing infertility can be realized.

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Amylophagia during Pregnancy: Some Maternal and Perinatal Correlations

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Amylophagia is a type of pica or perverse craving for and ingestion of starch, often to the exclusion of other dietary items. The Argo brand of laundry starch seems to be preferred, at least in the Chicago area.

Deleterious effects attributed to starch ingestion during pregnancy include anemia (1, 2) toxemia (3), and an increased "perinatal casualty rate" (4). The apparent relation between amylophagia and iron deficiency anemia in obstetric patients has been emphasized in previous reports from the Cook County Hospital in Chicago (1, 2). In contrast with the study reported by O'Rourke (3), however, our earlier study did not demonstrate a statistically significant association between pica and toxemia of pregnancy (5). Our efforts, however, were directed primarily toward clarification of the relation between pica and anemia. The present study was undertaken to evaluate the association between amylophagia during pregnancy and the maternal and perinatal outcome of pregnancy.

Materials and Methods

Except for patients with third-trimester bleeding, which could be expected to alter the hematologic status, each gravida within 4 weeks of the estimated date of confinement admitted in active labor to Cook County Hospital during daylight hours in the 3-month interval between October 1 and December 31, 1969 was included in the study.

A standard interview was conducted by the same interviewer. When rapport had been established, questions pertaining to starch ingestion were asked, after which a venous blood sample was obtained for a complete blood count.

Subsequent to obstetric delivery, the patient's hospital record was reviewed for the outcome of labor and delivery. The data were keypunched, verified, and stored for later analysis. The chi-square test was used for comparing frequency distributions shown in the accompanying tables. Results were considered significant at $P < .05$.

Results

Table I gives a description of the study population by race, parity, and history of starch ingestion during pregnancy. From the original population of 625, two

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American Indians were excluded from analysis because they represented the only respondents in a racial category other than black or white. Of the remaining 623 women, 526 (84.4%) were black. Multiparas numbered 403 (64.7%) among the 623 women. One out of four pregnant women gave a history of starch ingestion during the pregnancy; all the starch eaters were black. White women were excluded from analysis as shown in the remaining tables because they were not at risk of outcome associated with starch ingestion. Although the prevalence of starch ingestion was slightly higher for black multiparas than black primiparas, the difference was not statistically significant.

The average amount of starch ingested each day as reported by the patients ranged from a "handful" to one box or more (Table II). About half the patients reporting starch ingestion ate half a box or more daily, and one in five ingested a full box or more. The difference in amount of starch ingested by primiparas versus multiparas was not statistically significant.

When the study population was divided into two groups, those who reported starch ingestion and those who did not, anemia (hematocrit <30) was twice as frequent among the starch eaters, this difference being significant at $P < .01$ ($x^2 = 6.8$, df = 1; Table III).

TABLE I

*Distribution of Population and Prevalence of Starch Ingestion by Race and Parity**

Race and Parity	All Patients		Patients Reporting Starch Ingestion	
	Number	Percent	Number	Percent
White				
Primiparas	24	3.8	—	
Multiparas	73	11.7	-	
Black				
Primiparas	196	31.5	50	25.5
Multiparas	330	53.0	102	30.9
Total	623	100.0	152	24.4

* Parity based on completion of the present pregnancy.

TABLE II

Amount of Starch Ingested Daily by Parity

Daily Starch Ingestion	Primiparas		Multiparas	
	Number	Percent	Number	Percent
Handful	21	42.0	37	36.3
One-fourth box	10	20.0	20	19.6
One half box	11	22.0	21	20.6
One box or more	8	16.0	24	23.5
Total	50	100.0	102	100.0

Despite the increased prevalence of anemia among the starch eaters, a significant adverse effect on the course of labor was not demonstrated for women who practiced amylophagia compared with those who did not (Table IV).

We compared the prevalence of toxemia among starch eaters and non-starch eaters in our study population (Table V). Although the rates of diagnosis of this condition and of treatment with magnesium sulfate were slightly higher among the starch eaters (when controlled for the effect of parity), these differences were not significant in this relatively small population.

TABLE III

Hematocrit Values by History of Starch Ingestion

Hematocrit (%)	Starch Eaters		Non-starch Eaters	
	Number	Percent	Number	Percent
29 or Less	18	11.8	20	5.3
30-34	84	55.3	131	35.0
35 or More	50	32.9	223	59.6
Total	152	100.0	374	100.0

TABLE IV

Characteristics of Labor by Maternal Starch Ingestion During Pregnancy

Characteristics	Starch Eaters		Non-starch Eaters	
	Number	Percent	Number	Percent
Induction of labor				
Yes	4	2.6	14	3.7
No	148	97.4	360	96.3
Augmentation of labor				
Yes	7	4.6	19	5.1
No	145	95.4	355	94.9
Duration of labor (hrs)*				
5 or less	18	12.6	52	14.9
6-12	53	37.1	95	27.3
13–24	61	42.6	169	48.6
25 or more	11	7.7	32	9.2
Dysfunction of labor				
None	122	80.2	295	78.9
Prolonged latent phase	8	5.3	25	6.7
Primary dysfunctional labor	3	2.0	8	2.1
Secondary arrest	19	12.5	46	12.3
Intrapartum or postpartum hemorrhage				
Yes	3	2.0	10	2.7
No	149	98.0	364	97.3
Total	152	100.0	374	100.0

* Excludes patients with unknown duration of labor.

TABLE V

Prevalence of Diagnosis of Preeclampsia and of Treatment with Magnesium Sulfate by Parity and History of Starch Ingestion

Parity and Starch Ingestion	All Patients	Patients with Preeclampsia		Patients Treated with $MgSO_4$	
		Number	Rate/100	Number	Rate/100
Primiparas					
Starch	50	13	26.0	12	24.0
No starch	146	34	23.3	28	19.2
Multiparas					
Starch	102	8	7.8	6	5.9
No starch	228	16	7.0	8	3.5
Total	526	71	13.5	54	10.3

TABLE VI

Birthweight and One-Minute Apgar Score of Infants by History of Maternal Starch Ingestion During Pregnancy

Characteristics	Starch Eaters		Non-starch Eaters	
	Number	Percent	Number	Percent
Birthweight (grams)*				
2500 or Less	25	16.9	34	9.6
2501 or More	123	83.1	319	90.4
Apgar score (1 minute)				
4 or Less	1	0.7	10	2.7
5–7	10	6.6	30	8.0
8 10	141	92.7	334	89.3
Total	152	100.0	374	100.0

* Excludes infants of multiple birth or unstated birthweight.

Table VI shows two indicators of perinatal outcome associated with maternal amylophagia during pregnancy. The prematurity rate (based on infant birthweight of 2,500 gm or less) among starch eaters was almost two times that of patients who did not report amylophagia during pregnancy ($\chi^2 = 5.29$, $P < .05$). Nevertheless, the difference in the one-minute Apgar scores recorded between the two groups of infants was not significant.

Discussion

The interviewer, a white male medical student,* had the impression that many patients were reluctant to admit to the practice of amylophagia, although most "knew of it." Thus, the possibility exists that some patients were too embarrassed to acknowledge starch eating, and therefore denied it while actually doing so.

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* Dr. Cary Rosenberg, deceased.

However, since the history of starch ingestion was obtained during labor, before knowledge of the outcome, this prospective methodology avoided the problem of selective reporting by the patient based on the type of outcome. Finding the true incidence of amylophagia may be related to the ability to establish a nonthreatening type of rapport with the patient during the interview (4).

Among the variables studied, maternal starch ingestion during pregnancy was significantly associated with a higher risk of anemia and of prematurity based on birthweight. Our material supports the major findings in the unpublished work of Dunston (4). Whether such association is causal cannot be stated at present since the two populations (starch eaters and non-starch eaters) may well have differed in important ways other than in the practice of amylophagia. Maternal height and weight, or history of cigarette smoking, for example, are known variables associated with birthweight, but these were not recorded in our protocol.

We were unable to confirm the significantly higher incidence of toxemia among starch eaters as suggested by O'Rourke and his associates among patients who were mainly clay eaters (3). Various forms of pica may produce unique changes; the higher incidence of toxemia among the pica practitioners in O'Rourke's study may be attributable to the ingestion of dirt. O'Rourke did not subdivide his patient population into nulliparas and multiparas; since toxemia of pregnancy is primarily a disease of the nulliparous patient, a direct comparison of these diverse populations is not possible.

Conclusion

The practice of amylophagia during pregnancy is associated with increased prevalence of maternal anemia and low birthweights among the infants. Apparently there is no relation between the clinical course of labor or the frequency of preeclamptic toxemia with the practice of amylophagia. Further study is needed to ascertain whether the association between amylophagia during pregnancy with anemia and prematurity may be cause and effect.

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Production of Disseminated Intravascular Coagulation in Monkeys by Injection of Cell-Free Extracts of Placenta

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Disseminated intravascular coagulation often leads to widespread hemorrhage as a result of a low fibrinogen level and defibrination of the blood. In the pregnant patient such a situation occurs in a variety of circumstances, including abruptio placentae, retention of a dead fetus, septic abortion, and termination of pregnancy by instillation of hypertonic saline. The high proportion of deaths among patients suffering from "amniotic fluid embolism" also has been attributed to disseminated intravascular coagulation. However, the concept of "amniotic fluid embolism" itself is in doubt since experimental studies have shown that infusion of amniotic fluid in quantity may be innocuous in the primate (1). Both the placenta and the decidua are known to contain thromboplastin-like materials in high concentration (2). These substances have been considered as playing an essential role in bringing about postpartum hemostasis following the separation of the placenta (3, 4). At the same time, entry of these thromboplastin-like materials in large amounts into the general circulation may be implicated as the mechanism responsible for disseminated intravascular coagulation as an obstetrical complication.

The present study was designed to investigate the effects of administering cell-free extracts of placental tissue by intravenous injection to puerperal and juvenile rhesus monkeys upon the vital signs, the acid-base and respiratory gas state of the arterial blood, and the concentration of fibrinogen in the blood. The possibility of preventing the intravascular coagulation which follows the administration of placental extract by the prior use of heparin was also investigated, as were the effects of repeated injections of placental extract.

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Material and Methods

Thirteen rhesus monkeys were used. Nine were adult females within two hours after the surgical delivery of their near-term fetuses, i.e., on the 159th to 161st day of gestation. The body weights of these early postpartum females ranged from 5.8 to 9.3 Kg. The remaining four animals were juveniles which weighed 3.1 to 5.1 Kg. All animals were food deprived for 24 hours prior to the experiment, but water was allowed *ad libitum*. Each animal was anesthetized with IV sodium pentobarbital, 35 mg/Kg of body weight. A polyethylene catheter was inserted into a femoral artery and a femoral vein. The arterial blood pressure was recorded continuously using the polyethylene catheter filled with isotonic saline and connected to an impedance-type pressure transducer. Stainless steel ECG leads inserted subcutaneously over the precordium and in the tissues of the left hind limb were connected to an amplifier. The heart rate was recorded continuously using a cardiotachometer activated by the R-wave of the electrocardiogram. The respiratory excursions were recorded using an air-filled rubber bag mounted over the thorax and connected through plastic tubing to a pressure transducer. A polygraph recorded all channels of information.

The composition of the arterial blood was determined before the administration of any tissue extract and 3, 15, and 30 minutes afterwards. The oxygen tension was assayed using a polarograph, and the pH by a glass electrode. The concentration of fibrinogen of whole blood was determined using the ammonium sulphate precipitation method. Blood samples for fibrinogen determination were obtained before and thirty minutes after the administration of tissue extract.

Fresh placental tissue of near-term rhesus monkey fetuses was weighed, a volume of isotonic saline added equal to the weight of the tissue, and the mixture homogenized. A cell-free extract was then prepared by centrifuging the homogenate at 2000 *g* for 10 minutes. The entire supernatant was injected into the catheter in the femoral vein in all animals. The extract injected represented a range of concentrations of 10–1000 mg of placental tissue per kilogram of body weight of the animal injected. Only freshly prepared extracts were used.

In 12 instances in six postpartum animals and in two juveniles, the extract was injected over a 60-second interval. In two other instances, it was infused more slowly (over 3 and 7 minutes) in quantities of 10 and 160 mg/Kg/min respectively. Extracts of 370 and 660 mg of placental tissue were injected over 20 and 33 seconds in two other instances.

Three animals received multiple infusions separated by thirty minute intervals. One juvenile received an extract of 10 mg placental tissue/Kg of body weight twice; a second postpartum animal received 1000 mg/Kg twice. A third animal received a total of four infusions which contained 10, 100, 100, and 1000 mg of placental extract per kilogram of body weight at intervals of 47, 70, and 30 minutes respectively.

Heparin (2000 units) was administered intravenously to two postpartum and one juvenile animal in the five minutes prior to the injection of placental extract. The abdominal aorta and inferior vena cava were surgically exposed in one animal before 1000 mg/Kg of placental extract was administered intravenously.

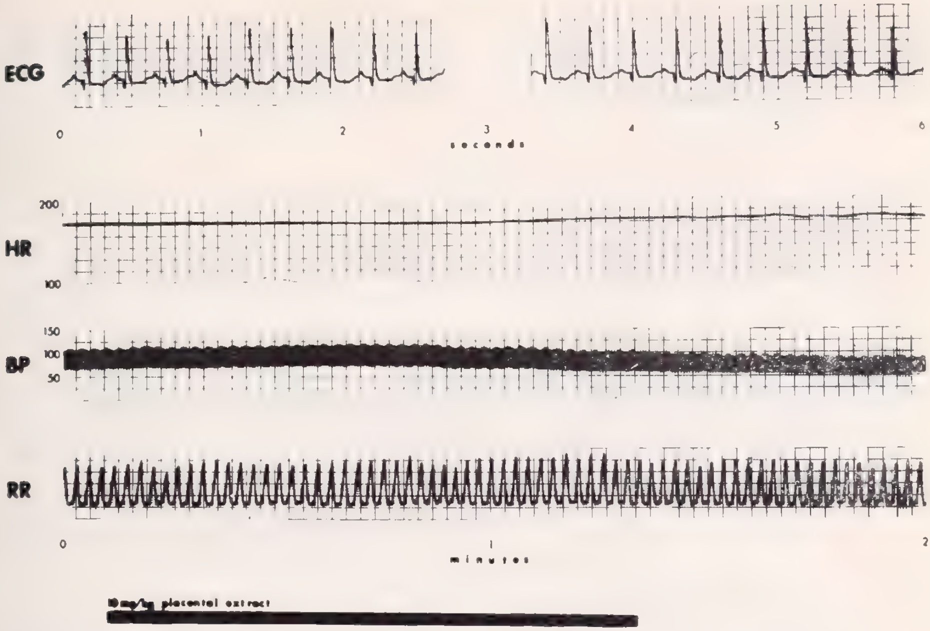

FIG. 1. Respiratory rate (RR), blood pressure (BP), heart rate (HR) and electrocardiogram (ECG) during injection of 10 mg/Kg placental extract over 74 seconds.

Results

Blood pressure: The effect upon the blood pressure was dose related. The injection of 10 mg/Kg of placental extract over 74 seconds into a postpartum animal produced a slight decrease in the systolic and diastolic blood pressures with a narrowing of the pulse pressure (Fig. 1). A larger dose (100 mg/Kg), injected over 60 seconds into the same animal 47 minutes later, led to profound hypotension and a major reduction in pulse pressure (Fig. 2). However, all values returned to their preinjection levels within ten minutes. The effect of this dose upon the blood pressure was slightly greater when it was not preceded by a prior injection of a lower dose of placental extract. Administration of 1000 mg/Kg of placental extract over one minute to another postpartum animal first caused a blood pressure elevation which lasted 10 seconds (from 135/80 to 152/92 mm Hg). This was followed by a precipitous decrease leading to disappearance of the arterial blood pressure by the time of the completion of the injection. Three minutes later the pulse pressure gradually began to reappear, and by thirty minutes the blood pressure had returned to 100/70 mm Hg.

The administration of 100 mg/Kg of placental extract following a prior injection of the same amount 60 minutes earlier did not lead to any significant change in the arterial blood pressure (Fig. 3). The injection of heparin (2000 units) 5 minutes before the injection of placental extract also prevented the blood pressure changes which have been described above (Fig. 4).

The infusion of 160 mg/Kg/min of placental extract extended over a 3-minute period produced a lowering of blood pressure beginning at about 15 seconds after

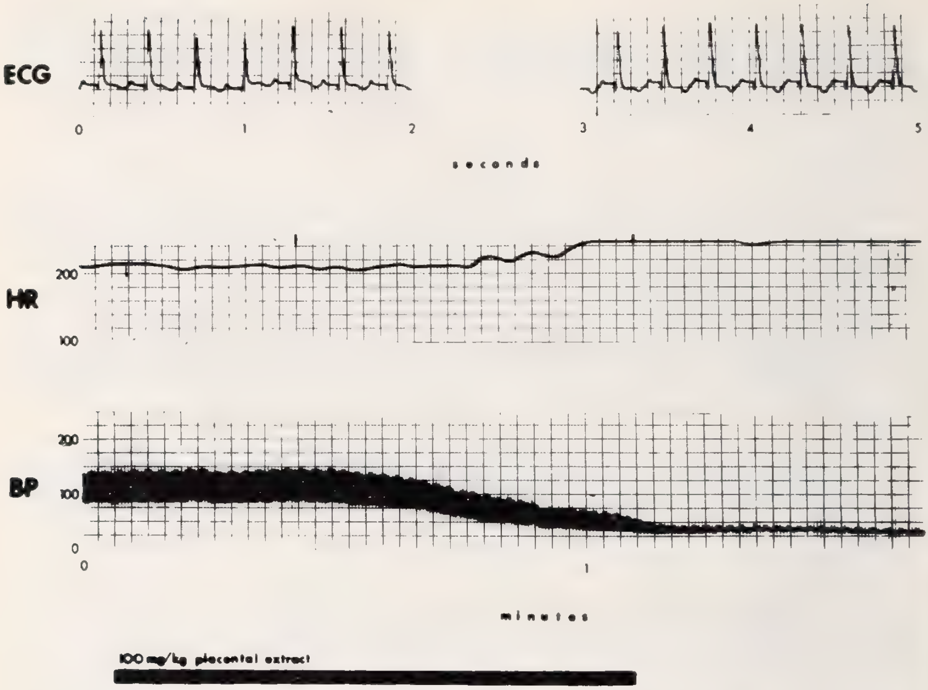

FIG. 2. Blood pressure, heart rate and electrocardiogram during injection of 100 mg/Kg placental extract over 60 seconds.

the start of infusion and leading to the decline of blood pressure to zero levels by 35 seconds. However, this disappearance of blood pressure was short-lived. The blood pressure began again to recover while the infusion was still in progress and reached 98/42 mm Hg by the end of infusion. This blood pressure compares with a preinfusion pressure of 120/80 mm Hg.

The abdominal aorta and inferior vena cava were surgically exposed in one animal before 1000 mg/Kg of placental extract was injected over 60 seconds. The pulsations in the aorta and its tributaries ceased entirely within 30 seconds. Respirations also disappeared by the end of the injection. When these exposed blood vessels were opened at this time, their lumina were filled throughout their extent with congealed blood.

Heart rate: The dose levels of 10 and 100 mg/Kg of body weight of placental extract produced brief episodes of tachycardia of varying extents (Figs. 1 and 2). Administration of 1000 mg/Kg also caused a short-lived increase in heart rate from a baseline of 176–220 beats/min, and this was associated with a brief increase in blood pressure. The early tachycardia was followed by an interval of bradycardia characterized by heart rates as low as 100 beats/min. As gasping reappeared following a period of respiratory arrest, as described below, the heart rate also recovered and ultimately remained in the range of 220–240 beats/min. Injections of placental extract which followed either previous injections of placental extract or of heparin failed to produce any significant changes in heart

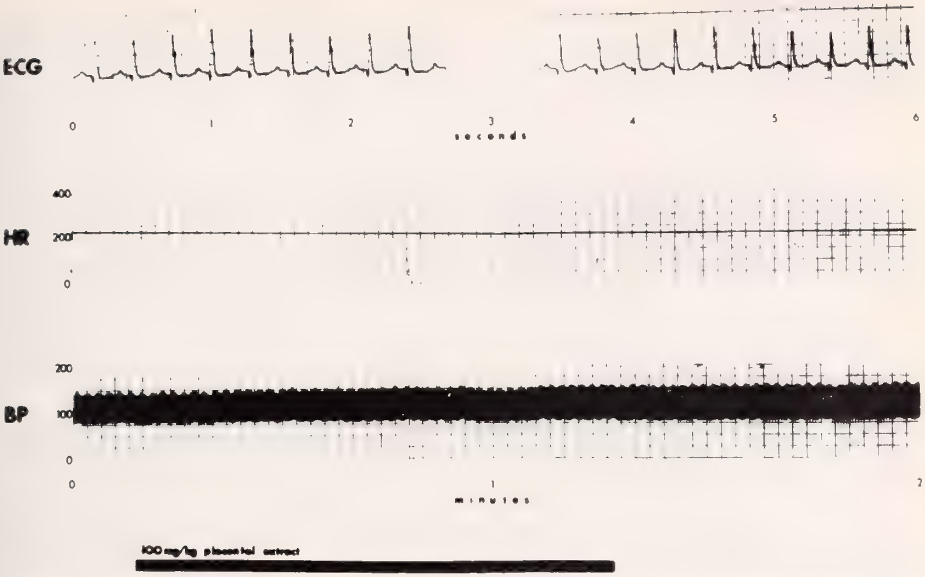

Fig. 3. Blood pressure, heart rate and electrocardiogram during injection of 100 mg/Kg placental extract following a previous injection of the same amount.

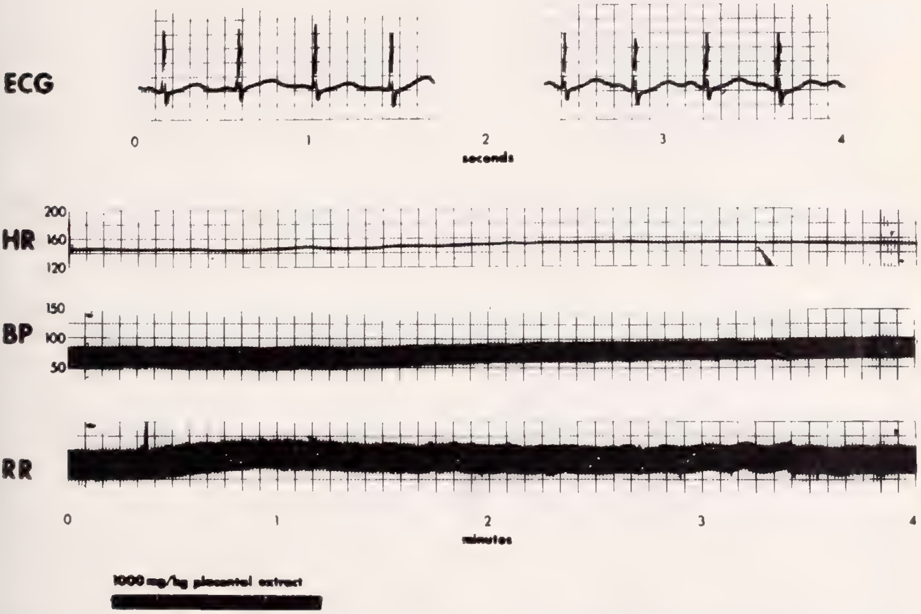

Fig. 4. Respiratory rate, blood pressure, heart rate and electrocardiogram during injection of 1000 mg/Kg placental extract preceded by administration of 2000 units of heparin.

rate (Fig. 4). Placental extracts, when given as more prolonged infusions, as described above, caused decreases in heart rate from 156 down to 100 beats/min. The heart later recovered to a rate of 190–200 beats/min.

Electrical activity of the heart: The electrical activity of the heart remained unaltered during the injection of small amounts of placental extract (10 mg/Kg) and during the injection of extracts which followed the previous administration of either placental extract or of heparin. The injection of 100 mg/Kg of placental extract over a one minute period produced minor, while the administration of 1000 mg/Kg produced profound changes in the P-Q segment. These consisted of decreases in amplitude of the R-wave and increases in amplitude of the T-wave. In some instances, the amplitude of the T-wave exceeded that of the R-wave. The infusion of placental extract produced slight decreases in the amplitude of the R-wave and slight elevations of the S-T segment.

Respiratory rate: Changes in respiratory rate during the infusion of placental extract were dose-related, and corresponded to the changes observed in blood pressure. The administration of doses which produced disappearance of pulse pressure also produced cessation of breathing after a brief episode of gasping. The period of respiratory arrest, in turn, was followed by another series of gasps of increasing frequency and decreasing depths until a normal pattern of breathing was reestablished. The reappearance of the first gasp following the period of apnea coincided with the reappearance of a discernible pulse pressure. As the normal respiratory pattern was restored, the pulse pressure widened and ultimately returned to the preinjection amplitude. If a small amount of placental extract was injected or if a previous injection had already been given, a brief increase in depth of respiration was followed by a transient increase in rate. The injection of placental extract which was preceded by the administration of heparin did not produce any change in respiratory pattern (Fig. 4).

Oxygen tension and acid-base state: Prior to the injection of placental extract, the oxygen tension ranged from 86–124 mm Hg, and the pH value ranged from 7.32–7.45. Whenever the injection of placental extract produced a disappearance of the blood pressure, samples of blood could not be obtained until the blood pressure was reestablished. In those cases where serial arterial blood samples were obtainable before and after placental extract injection, no significant changes in pH or oxygen tension of the arterial blood could be demonstrated.

Fibrinogen concentration: The concentration of fibrinogen in the arterial blood prior to the administration of placental extract ranged from 318–718 mg%, with a mean value of 489 mg%. Following the administration of extract, the fibrinogen concentration decreased markedly. In the case illustrated in Figure 1, the fibrinogen concentration was 518 mg% prior to injection of 10 mg/Kg of placental extract over 74 seconds, and 168 mg% three minutes afterwards. When a second injection was given to the same animal 47 minutes later, with a 10-fold increase in dosage (100 mg/Kg over 60 seconds), the fibrinogen concentration further decreased to 32 mg% (Fig. 2). Following the administration of the same dose of placental extract 60 minutes later, the concentration of fibrinogen was too low to be measurable (Fig. 3).

The infusion of placental extract for three minutes in a dose of 160 mg/Kg/min produced a decrease in fibrinogen concentration from 539 to 197 mg%. A transient respiratory arrest appeared, associated with a brief disappearance of the pulse pressure.

Discussion

The intravenous administration of the cell-free supernatant obtained from a homogenate made of fresh placental tissue can produce adverse effects on circulation and respiration. When a low dosage is administered (10 mg/Kg), either no effect is observed or a transient episode of slight lowering of blood pressure may be seen. When the dosage is increased (to 100 mg/Kg), marked decreases in blood pressure appear associated with changes in respiration. Finally, with a further increase in dosage, the blood pressure decreases to essentially zero levels (or to levels equal to those in the surrounding tissues) and the animal becomes apneic. However, within a few minutes, the circulatory and respiratory functions begin to recover and in most instances are restored to the preinjection levels within 10-15 minutes. The observed cardiovascular changes are most compatible with a decrease in cardiac output brought about by an impaired venous return. These changes in turn must be caused by alterations in the physical properties of the blood produced by the action of the injected thromboplastins. This contention was verified by a direct examination of the contents of medium- and large-sized systemic blood vessels including the vena cava and aorta and various other, smaller blood vessels in the abdomen, chest, and extremities. When examined at the time when the arterial blood pressure had declined to tissue pressure levels, the contents of these vessels consisted everywhere of congealed blood which could be extracted from the incised vessels with forceps as long casts which took the form of the containing blood vessels and their ramifications. It is noteworthy that tachypnea which characteristically is present in clinical situations associated with pulmonary emboli did not appear. Rather, the situation was one of a decreasing ventilatory activity leading to apnea in cases where large doses of extract were injected. Additionally, the ECG failed to indicate the development of hypertension in the pulmonary circulation. The marked depression of respiratory activity observed may be explained best by an impaired blood flow to the cerebral respiratory centers as a part of the generalized reduction in tissue perfusion.

The injection of placental extracts produced a reduction in the fibrinogen concentration in the blood, the degree of which was proportional to the administered dosage. At the lower dosage level, even though the circulatory changes were minimal, the fibrinogen levels decreased by as much as 70%. In instances where the amount of extract administered was sufficient to cause cessation of blood flow, the concentration of fibrinogen following recovery of blood pressure was so low as to be undetectable. The finding of a total consumption of fibrinogen with a generalized intravascular coagulation was anticipated. What was surprising, however, was that a dose of thromboplastin, sufficient to produce a total solidification of blood throughout the body, was not lethal. The rapidity with which hydrolysis of fibrin within the lumina of blood vessels can occur is also illustrated in the experiments in which 10 mg/Kg of placental extract was injected. In spite of the fact that as much as 70% of the fibrinogen was removed from the circulating blood within 3 minutes, this was accompanied by minor changes in blood pressure, heart rate, and pO_2 and pCO_2 of the arterial blood.

Most of the findings obtained in the present study with primates immediately after delivery closely parallel the observations pertaining to the effects of the IV injection of thrombin into non-puerperal animals (5). Thus, the degree of hypotension induced and the outcome with respect to survival were dose-related in the studies with thrombin, as in the present study. Dose levels of 166 or 275 units/Kg of thrombin proved lethal whereas lower dosages produced only transient episodes of hypotension.

Disseminated intravascular coagulation and hypofibrinogenemia resulting in severe hemorrhage in obstetrical patients have been observed mainly as the result of abruptio placentae (6). However, with the increasing use of hypertonic saline instillation into the amniotic cavity to induce second-trimester abortion, reports of serious disturbances in coagulation and the development of hemorrhages resulting from hypofibrinogenemia and the reduction of other coagulation factors have appeared (7–10). A clinically significant hemorrhagic diathesis has been reported with an incidence of 1:1500 cases (7). In abruptio placentae as well as with saline abortion, various degrees of destruction of trophoblastic tissue take place (11). The present results support the view that the disseminated intravascular coagulation and hypofibrinogenemia which follow abruptio placentae or saline abortion occur whenever a large amount of thromboplastin-like material is released from the trophoblast or decidua and enters the systemic circulation of the mother.

The usually fatal syndrome of "amniotic fluid embolism" has been ascribed to disseminated intravascular coagulation which is brought about by the thromboplastic activity of amniotic fluid which may enter the circulation (12). This interpretation has not been confirmed in the rhesus monkey, in which a large amount of fresh autologous amniotic fluid was infused intravenously to the mother (1). However, "amniotic fluid embolism" frequently occurs in relation to precipitous labor and in cases of uterine hypertonus or rupture (13), and it might be envisaged that the resulting circulatory embarrassment of the trophoblast could lead to its necrosis and the leakage of thromboplastin-like material into the amniotic fluid or more directly into the maternal circulation.

The administration of small amounts of placental extract inhibits the adverse effects of the subsequent injection of large amounts of the same material. This is due partly to the decrease in fibrinogen concentration in the plasma and partly to the anticoagulant properties of the fibrin split-products produced. Such a circumstance, although protective with respect to the occurrence of intravascular clotting, leads to high risks with respect to bleeding. Such a situation often occurs in patients who exhibit hypofibrinogenemia as a result of the prolonged retention of a dead fetus, following the premature separation of the placenta, or the intra-amniotic injection of hypertonic saline.

The administration of heparin in low dosages prior to the injection of placental extract similarly prevents intravascular coagulation and eliminates the adverse circulatory effects of this process. However, the role of heparin therapy in obstetric patients with intravascular coagulation disorders is controversial (14, 15). Heparin therapy would be of clear value if initiated prior to the influx of thromboplastin-like material into the systemic circulation. Since this is rarely possible in a clinical situation, rapid evacuation of the thromboplastin-releasing products of conception must remain the primary therapeutic goal whatever the inciting cause. However, if this is not immediately feasible and further influx of large amounts of thromboplastin into the systemic circulation is anticipated, it may be possible to prevent further defibrination by administering heparin.

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Modern Use of the Laminaria Tent

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The use of the laminaria tent to effect dilatation of the cervix is an old therapy described both in the American and British medical literature of the second half of the nineteenth century (1, 2). Use of the device apparently was widespread. Around the turn of the century, the medical literature contained reports of deaths associated with the tent, usually caused by sepsis or perforation of the uterus (3). Following these reports, the utilization of laminaria tents decreased, and they disappeared from medical practice in the United States. In Europe and in Japan, however, physicians continued to employ them as efficient cervical dilators for various purposes, notably preceding induced abortion.

Two major factors accounted for the decreased interest in the laminaria tent in the United States. First, restrictive abortion laws of the later half of the nineteenth century minimized the need for the device; secondly, no method was available for sterilizing the tent before insertion. Recent liberalization of abortion practices and the discovery that gas sterilization effectively prepares the tent for safe medical use have combined to encourage the reintroduction of the tent into American medicine. Widespread use has resulted, especially as an aid to various abortion techniques.

The laminaria tent is manufactured from one of several species of seaweed which grows in cold ocean waters. The stem of the seaweed is harvested by divers, quickly dried on shore, and then cut and shaped into appropriate form. The material is markedly hygroscopic and swells to three or four times its original diameter upon contact with fluid (Fig. 1). The seaweed is cut into lengths of about 6–8 centimeters and is supplied in various diameters. The medium size has a diameter of about 3–4 mm. A hole is drilled in one end of the tent and a string inserted through it to provide traction. Recently, a button-like piece of plastic has been slipped on the distal end of the tent to prevent upward migration in the cervix (Fig. 2). The tent thus prepared is packaged and gas-sterilized.

Insertion into the cervix is performed a minimum of 4–6 hours before dilatation is needed for the operative procedure. Hale and Pion (4) have shown that adequate dilatation occurs in this time interval, although further dilatation can be expected over the next few hours. To insert the laminaria tent, it is usually necessary to provide countertraction on the cervix with a tenaculum. Paracervical anesthesia is rarely needed. After grasping the cervix with the tenaculum, a sound is introduced into the cervical canal both to confirm the direction of the canal already determined by bimanual pelvic examination and to prepare a route for the laminaria insertion. A tent is inserted until only the tip is visible at the external cervical os. Rarely, a second or third tent is simultaneously inserted to

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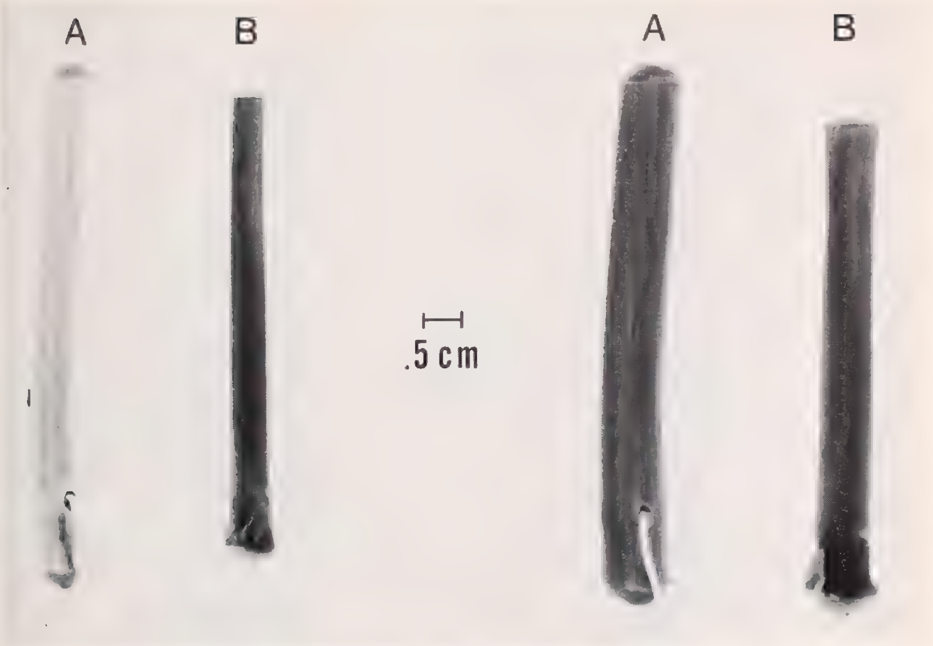

FIG. 1. Two types of laminaria tents: A. unflared tip; B. flared tip. Left, unused; right, full expansion after placement in water. (Reprinted from Niswander, K.: California Medicine, 119:11, 1973 with permission of publisher.)

increase the amount of dilatation. Passage of the tent through the internal cervical os is absolutely essential for success. The vagina is cleansed with an antiseptic before insertion, but no antibiotics are administered. The patient is not required to remain in the hospital following insertion, and may return later for the needed operative procedure. Many patients experience mild cramps over the next few hours, but this symptom is rarely severe. At the time of the operative procedure the tent is removed, preferably by grasping the tent itself rather than the trailing string. Reports of upward migration of the tent into the uterine cavity or beyond reach in the cervix have been published and will be discussed.

The major current use of the laminaria tent is to prepare a cervix for abortion. Investigators have found the device useful both with early suction abortion and with mid-trimester intraamniotic hypertonic saline or prostaglandin abortion. The purpose of the device is to provide slow dilatation of the cervix and thus minimize cervical damage from rapid instrumental dilatation or hypertonic uterine contractions. The tent greatly simplifies the technical difficulties of suction abortion and it apparently shortens the injection-abortion interval with late abortions. The hazards of the laminaria tent are minimal.

Use with early abortion

We have used the tent preceding early suction abortion in over 1,000 patients. A report on the first 327 patients has been published (5). We insert the tent the

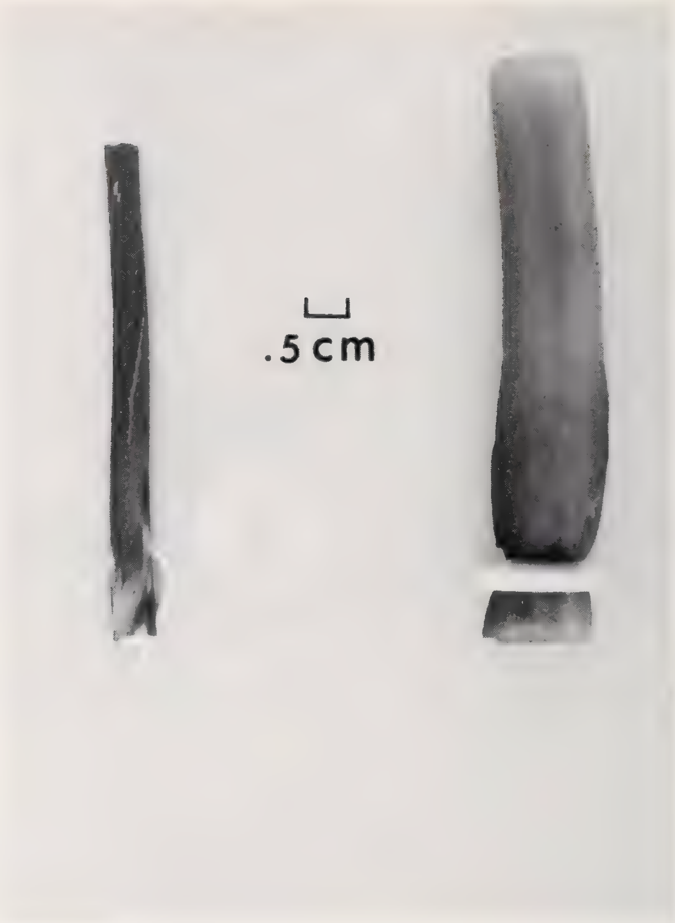

FIG. 2. Laminaria tent with "button" to prevent upward migration: left, before use; right, fully expanded.

afternoon before the planned surgery. The patient is allowed to go home after the insertion. The tent has made it possible to eliminate general anesthesia for suction abortion, since most of the necessary cervical dilatation is accomplished by the tent. We use a preoperative injection of subcutaneous morphine sulfate, 10 mg, and diazepam, 5 mg, or meperidine, 50 mg, and hydroxyzine, 100 mg for analgesia one to two hours before the procedure. Paracervical anesthesia is induced prior to operation. The typical patient experiences little or no pain with the suction abortion. If the tent has failed to produce sufficient dilatation (Table I), cramps usually accompany the needed additional dilatation. Blood loss has been minimal (Table II) even though not infrequently we perform the procedure up to 14–15 weeks gestation. The patient is not admitted to the hospital for the abortion but is treated as an outpatient.

Complications occurred in 17 of the first 327 patients (5.2%). Two patients developed small cervical lacerations from the tenaculum used to insert the lami-

TABLE I

Cervical Dilatation at Time of Operation (5)

Weeks of Gestation	Dilatation (millimeters)			
	6 or less	7 to 8	9 to 10	11 or more
10 or less	9%	25%	46%	20%
11 to 12	4%	12%	47%	37%
13 or more	6%	13%	37%	44%

TABLE II

Blood Loss Related to Duration of Pregnancy (milliliters) (5)

Weeks of Gestation	0–25	<50	<100	<150	<200	<250	<300	>300
10 or less	12%	43%	33%	6%	5%	..	1%	0.5%
11 to 12	3%	21%	47%	8%	17%	2%	..	1%
13 or more	..	..	17%	22%	17%	11%	5%	28%

naria tent. Trachelotomy was required in 3 patients to remove a tent which could not be reached for extraction because of upward migration (6). In each case the procedure was a simple one, although two of the patients experienced postoperative fever. Ten patients developed endometritis or were diagnosed as an incomplete abortion during the first few postoperative days; of these, six were admitted for a curettage. None was seriously ill. Two additional patients suffered an unexplained postoperative fever and in one of these the uterus probably had been perforated but the accident not recognized at surgery. She did well and recovered rapidly after a mild 2–3 days' illness.

The migration of the tent upward toward the uterine cavity in 3 of our reported patients (and a subsequent one unreported) requires comment. The first 3 cases occurred with the use of a tent of uniform diameter throughout. Another tent currently available is slightly flared at the distal tip, and we speculated that this slight flaring might prevent upward migration (Fig. 1). The latest upward cervical migration, however, occurred with a flared tent. The recent addition of a "button" attached to the outside of the distal end of the tip prevents this complication (Fig. 2). Removal of the tent by trachelotomy or by extraction from the uterine cavity with a sponge forceps is satisfactory treatment for this unusual complication (7).

Hale and Pion (4) compared the incidence of complications among 626 patients aborted by suction curettage without tent insertion with 205 patients aborted in the same fashion but with a laminaria tent inserted the day before surgery. Six percent of patients in the former group of 0.5% in the laminaria group suffered cervical laceration which required suturing. In each group, 0.9% of patients developed postoperative febrile morbidity. There were no uterine perforations when the tent was used; two definite and two possible uterine perforations were recognized among the 626 patients in whom the tent was not used. The operating time was shorter by a mean of 4.7 minutes when the tent was used.

Use with mid-trimester abortion

A number of reports have been published of experience with the laminaria tent as an aid to mid-trimester abortion induced either with intraamniotic hypertonic saline or prostaglandin.

While most authors have reported a decrease in the mean injection-abortion interval when the laminaria tent is used with intraamniotic hypertonic saline, in some instances the decrease was small and not statistically significant. Hale and Pion (4) reported a decrease in the mean time interval from 28.5 hours to 20.7 hours if the tent was inserted before the hypertonic saline was injected and to 22 hours if the tent was inserted after the injection. Lischke and Goodlin (8) reported a similar decrease in their patients. Neither of these investigations controlled for parity. The experience in our clinic has been less favorable (9). Among 75 primigravidas (50 with the tent and 25 without the tent) who had intraamniotic hypertonic saline instillation and subsequently were treated with dilute intravenous oxytocin, the injection-abortion interval was reduced with the tent from 30.7 hours to 26.8 hours. This difference was not statistically significant. A higher complication rate occurred with the tent (40% versus 25%), but this increase also was not statistically significant. The complications in the laminaria tent group included a febrile reaction in 22% of the patients and a need for uterine curettage to complete the abortion in 18%.

Intraamniotic prostaglandin $F_{2\alpha}$* consistently produces abortion among patients in the mid-trimester. The mean injection-abortion interval is shorter than with hypertonic saline. Laminaria tents have been used with these patients in an attempt further to reduce this time interval and to minimize the risk of cervical laceration or uterine rupture. Stubblefield et al (10) reported a decrease in the mean injection-abortion interval among patients injected with 40 mg of prostaglandin $F_{2\alpha}$ from about 29 hours to 9.6 hours when the laminaria tent was used. Engle et al (11) treated 20 patients with tent insertion the night before the intraamniotic injection, but these investigators used only 15 mg of prostaglandin $F_{2\alpha}$. Intravenous oxytocin also was started just before the prostaglandin injection in this series. The median injection-abortion interval among primigravidas was 14.3 hours, and among multigravidas, 6.3 hours. Only 9 patients required analgesia for labor pain.

Golbus (12) inserted the laminaria tent just before the intraamniotic prostaglandin injection of 40 mg in 20 patients, while no tent was used in 20 matching patients similarly injected. The groups were alike in terms of maternal age, parity, and gestational interval. With no laminaria tent, the mean injection-abortion interval was 21.7 hours. With the tent, the mean interval was 15.0 hours. Golbus also reported that nearly half of the patients without tent insertion requested analgesia for labor cramps, while only a quarter of the tent patients required medication.

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* Prostin® (Upjohn).

Although we do not have a control population in our clinic with which to compare the laminaria tent group, the mean injection-abortion interval among our intraamniotic prostaglandin patients with the insertion of a laminaria tent 12–18 hours before the 40 mg injection also appears to be about 15 hours.

Discussion

The major effect of cervical insertion of the laminaria tent is gradual dilatation of the cervix, and this is accomplished primarily by hygroscopic swelling of the tent. Less swelling of the tent, with a resultant decrease in cervical dilatation, is seen if the tent is removed or is extruded early. Most of the necessary swelling occurs within 5–6 hours of insertion. The distended tent itself also produces uterine contractions, as demonstrated by Manabe et al (13). These investigators inserted a polyethylene tube transabdominally into the amniotic sac of mid-trimester abortion patients to measure intrauterine pressure. A laminaria tent was inserted into the cervix. After 12–24 hours, the cervical dilatation was sufficient to allow the placement of an extraovular metreurynter in the lower uterine segment to effect abortion. Before metreurynter insertion, uterine contractions were measured up to about 150 Montevideo units. The effect of the tent may therefore be mediated not only through cervical dilatation but also through uterine contractility.

Hale and Pion (4) inserted a laminaria tent into the cervix the night before a scheduled vaginal hysterectomy in nonpregnant patients. The resulting surgical specimens were examined in the laboratory. Microscopic changes in the cervix following laminaria tent use were limited to acute and chronic inflammatory reaction. Experience suggests the infrequency with which clinical infection can be expected following laminaria tent use.

The advantages of utilizing the laminaria tent before abortion include less cervical trauma from the subsequent abortion procedure, less need for anesthesia during the abortion, and a shortened operating time, or, in the case of mid-trimester patients, a shortened mean injection-abortion interval. The major disadvantages are the additional office visit required for insertion, the occasional upward migration of the tent, and the possibility of infection. Upward migration has not appreciably increased the operative difficulty. In such patients the cervix is always well dilated, and withdrawal of the tent from the endometrial cavity is usually easy.

Infection is apparently no more frequent when an operation to induce abortion is preceded by laminaria tent insertion into the cervix than when it is not. In clinical practice, the tent rarely has been allowed to remain in situ longer than 24 hours; longer use might increase the infection risk. No bacterial growth has been detected in tents prepared with gas sterilization before use, and only 3.3% of tents cultured after use grew organisms (14). Resterilization of used tents is apparently as effective as initial sterilization in preparing tents for use.

Other uses for the tents have been suggested but no reports of any large clinical experience for procedures other than for abortion have appeared in the literature. The tent may be useful in preparing the cervix for IUD insertion, radium insertion, or endometrial biopsy. Other uses will undoubtedly be reported.

Summary

Use of the laminaria tent to dilate the cervix preceding either early or mid-trimester intentional abortion has proved safe and efficacious. The device deserves widespread use.

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Humane Abortion Services: A Revolution in Human Rights and the Delivery of a Medical Service

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In 1955, when I began working at Mount Sinai as an assistant resident in obstetrics and gynecology, Dr. Guttmacher already was regarded as a pioneer in the field of providing abortion services. The Mount Sinai Hospital had an "Abortion Committee" which decided whether or not an abortion would be provided on request of a woman's physician. The decision was not taken lightly. Two gynecologists and a related medical specialist were in attendance at the meetings and each decision reached through almost a quasi-judicial procedure. Statements were required by two consultants who attested to the impact of a physical illness or the effects of pregnancy on a patient's mental status. Consideration of the issues sometimes was lengthy and occasionally quite stormy.

As the decade advanced, it became clear that maternal rubella infection in the first trimester affected the status of the fetus, and rubella also became an indication for first trimester abortion. The documentation of maternal rubella was rigorous, and often was difficult to prove. Each abortion continued to be regarded with awe, and there was an implied effort to keep the number of abortions low. The Mount Sinai Hospital itself feared being labeled an "abortion mill," and many members of the staff felt that Dr. Guttmacher had breached normal medical-moral discipline by allowing abortions to be performed at the hospital. Even Dr. Guttmacher himself occasionally voted against an abortion. While he bravely stood in the forefront of those who recognized the need for abortion, he still may have felt some inner constraint to prevent overutilization of abortion services, if only for the protection of the institution in which he worked.

The prevailing atmosphere of the fifties in medical institutions throughout the country was that induced abortion had to be "therapeutic" and needed to be performed only infrequently and then with great thought. The system was openly and obviously biased in favor of the rich. Wealthy women had less difficulty in obtaining the proper psychiatric or medical consultations required, and the advocacy of a private obstetrician. Few if any therapeutic abortions were done in city hospitals and then only under the direst of circumstances.

The general mental picture conjured up by the word "abortionist" was that of an unsavory individual, probably a medical derelict hooked on drugs, or an alcoholic, psychopathic in behavior, or someone otherwise driven to obtain money by the performance of outrageous services. Other images of abortionists consisted of unscrupulous beauticians, nurse midwives, and seamy underworld characters who for sufficient money would do anything to induce an abortion. The wards of municipal hospitals usually contained several women recovering

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from "septic spontaneous abortions." During the decade from 1959 to 1969 at the King's County Hospital, over fifty women died as the result of obviously induced abortions. It was quite clear that abortions were being done in the community despite the heavy prohibitions against their occurrence and the legal penalities applied to those caught performing abortions.

However, in the same decade there were physicians who believed that women were entitled to terminate their pregnancies if they felt that they should not have them. These doctors managed to find competent physicians in other areas or foreign countries who would perform abortions or would themselves induce uterine bleeding in the office and then send the patient to the hospital as a "spontaneous abortion." These men by and large were silent, and the number of abortions that they performed or referred was miniscule compared to the needs of women.

The victory in the struggle to provide contraceptive services in the municipal hospitals of the city of New York was an opening wedge for debate on the issues of liberalization of abortion services. Groups sprang up to help enact "liberal" or "reform" abortion laws. There were many partisans in favor of a liberalization of the law, and a model law was drawn up that would have permitted abortion on social grounds, to preserve the life and health of the mother in the broadest sense. These reform laws, however, still required the maintenance of an almost judicial system and the need for consultative services. Colorado, North Carolina, and California passed such laws in 1967. At about the same time, data began to accumulate on the safety and efficacy of the massive abortion activities in Eastern Europe and Japan. It became clear that the legal provision of abortion was infinitely safer than previously alleged. The feminist movement in the United States seized on the importance of gaining control of their bodies as a foundation for women's rights, and developed strategies for obtaining abortions, underground referral networks, and alliances with other groups that could help them obtain abortions.

In the early 1960's, many groups prepared for a long battle for abortion reform. Pat McGinnis wrote a famous paperback called *The Abortion Handbook*. In it, instructions were given as to how to fake a depression so that one could obtain a psychiatric opinion saying that an abortion was necessary to prevent suicide. The concept that women had to plead for an abortion was one that was destined to continue for several more years.

In 1967, the British Parliament enacted a liberal abortion law that allowed abortions to be performed to preserve the health of the mother. Though it had many drawbacks, including the necessity for obtaining physicians' signatures, consultations, and overnight stays in the hospital, it was a model law for a western society. At this time Britain stood alone among the Western European and North American countries in terms of having a relatively nonrestrictive abortion law.

In the United States the pressure for legal reform continued. An abortionist openly surfaced in Washington, D.C. and began to perform abortions on referral, basing his activities on a rather broad interpretation of an old Washington abortion statute. He was indicted, tried and the (judicial) decision by the Supreme

Court in his case allowed Washington to become one of the first centers for liberalized abortions in the United States. In New York, where attempts to pass a "reform" abortion law had met with defeat in Albany, a rather sudden reversal that astounded even its proponents permitted an extremely liberal law to pass in early 1970. The law became operational on July 1, 1970, and within a short interval, abortion services were supplied all over New York City, including municipal hospitals, and in many localities throughout the state.

The Washington decision and New York action resulted in areas in the country where women could go for abortions without the necessity of an elaborate petition to medical authorities. Finally, ruling on two cases brought before them, the United States Supreme Court handed down a decision in January 1973, the essence of which is quoted here from the statement on abortion by the American Public Health Association, that essentially granted women throughout the country the freedom to decide for themselves whether or not they wanted to have an abortion:

1. Until the end of the first trimester of pregnancy, a period in which the hazards of abortion are less than the hazards of childbirth, "the attending physician, in consultation with his patient, is free to determine, without regulation by the State, that in his judgment the patient's pregnancy should be terminated."
2. During the stage subsequent to the first trimester, the State may, if it chooses, "regulate the abortion procedure to the extent that the regulation reasonably relates to the preservation and protection of maternal health." The Court stated that examples of permissible state regulation are requirements as to the qualifications and licensure of the person who is to perform the abortion and as to the facility in which the procedure is to be performed (hospital, clinic, or place of less-than-hospital status) and the licensure of the facility.
3. For the stage subsequent to viability, the State may, if it chooses, regulate, and even proscribe abortion "except where it is necessary, in appropriate medical judgment, for the preservation of the life or health of the mother."

Within the space of fifteen years, a sweeping change had occurred and a firm legal base had been established for women not only to have contraception but also to have the option to terminate a pregnancy. Almost simultaneously, developments had taken place on the technology of performing abortions that allowed services to develop as the laws became liberalized. From Eastern Europe the vacuum aspirator had been brought to Great Britain, and Dr. Dorothy Kerslake demonstrated the ease and efficiency of vacuum aspiration as compared to a conventional sharp curettage. With Britain rapidly developing varieties of medical equipment designed to make abortions safer and more rapid, the Labor Foundation served as a catalyst to bring this technology to the United States. Dr. Lalor Burdick gave grants to several key physicians in the United States to develop and use the vacuum aspiration equipment. By the late 1960's, several manufacturers had developed reliable equipment that was available when the liberalized laws went into effect.

When it became apparent that New York State was going to have a liberal law, the Clergy Consultation Services moved rapidly to develop a non-profit facility that would provide women with abortions that would be dignified, empathetic, and safe, and recruited Hale Harvey to serve as first director of this clinic. Other "women's services" developed, often spearheaded by physicians who had been involved with the movement. Harvey Karman, a psychologist long associated with underground abortion service in the Los Angeles area, surfaced and disclosed several technologic advances intended to make abortion services even safer. At approximately the same time, PRETERM Washington, founded by Mr. Harry Levin and Nan McEvoy, both of whom have been concerned with the movement for liberalization of abortion laws for several years, opened its doors to provide a model facility in the Washington area. Other such centers developed throughout the country as the impact of the Supreme Court decision was felt. Planned Parenthood in New York City developed a model facility and Planned Parenthood-World Population later developed a seed fund to assist Planned Parenthood affiliates throughout the country in developing abortion facilities.

This has been the chronology of a struggle—the struggle of women to acquire the right to determine what they would or would not do if they became pregnant, and to control their own bodies. The Supreme Court decision has not ended the abortion controversy. It did not clarify the issue of abortions on minors without parental consent. A strong anti-abortion movement has sprung up throughout the country. The so-called Pro-Life Movement has mounted a stunningly impressive campaign to reverse the Supreme Court decision and in effect to return to the previous status quo. As meaningful and important as these decisions have been to women throughout the country, it is quite clear that for many people abortions are repugnant on moral grounds. Their efforts are continuing in this country to reverse not only liberalized abortions but also provisions of contraceptive service, sexual information and education programs, and all the issues that surround the questions of right to exercise one's sexual interest and control one's body.

What were the really revolutionary characteristics of the abortion movement? What can one say are the three things that are astounding for a field that requires a medical service?

1. The right of a woman to decide for herself what medical procedure she chooses to have, the right for her to decide what she would do with her body, the right for her to do this without "permission" from another authority (generally male).
2. A model under which consumer demand could produce a service that continually reduced its cost in response to pressure, something that was unusual if not unique for medical services.
3. Sufficient monitoring and observation of those services so that they would be carried out in the most humane and empathetic way possible.

An Overview of a Free-Standing Center

The free-standing center which sprang up to provide abortion services is an entirely novel means of delivering services. The centers, most of them for profit and run by physicians or entrepreneurs, remain an open, competitive market, responding to economic pressures, which is rather unusual for medical services. But over and above that is the fact that abortion services have been monitored by a number of groups. In many areas women's organizations continually have reviewed both the quality and the humaneness of the service. Planned Parenthood referral groups throughout the country as well as Clergymen's Counseling Services have provided a review body to insure the provision of quality services. It is a tribute to the potency of a consumer group that it could succeed in providing itself with a high quality, humane medical service at a reasonable price, and at the same time maintain some control over the quality of the service. There is no comparable example in the area of delivery of medical care.

Description of a Free-Standing Center

The free-standing center today has as dominant themes the concepts that a woman has the right to be treated with dignity and humanity, the right to know what is going to happen to her, and the right to obtain a high-quality medical service at a reasonable cost.

PRETERM, which operates abortion facilities in Washington, Boston, and Cleveland as well as participating with several other nonprofit centers in the provision of services, has consistently attempted to produce a model for delivery of abortion services that could be used as an example for delivering any medical service. What are the elements of these services? For one, specially trained telephone operators are provided so that even appointment-making is changed from the anonymous and impersonal style that exists in many clinics and hospitals to one in which a human contact can be made with somebody who is in crisis. Information can be obtained that will insure the least inconvenience and difficulties relating to arriving at a center and having an abortion performed, as well as conveying such information as will allay the anxiety and clarify the procedure to the caller. At PRETERM Washington, for example, there are no requirements relating to age of the woman, spouse consent, or any other legal encumbrances. The sole deciding factor that determines whether or not a woman is eligible for abortion is her ability to arrive at an informed consent that indicates to the staff that she has made the decision freely of her own will and understands the alternatives to and the risks and benefits of the procedure.

This is the sole requirement for women who are in good health. There are women whose physical condition is such that there would be an unwarranted risk taken if they were aborted in a non-hospital setting, and there are women whose pregnancies are too far advanced to have a first trimester vacuum aspiration. The question of medical eligibility is one that has been clarified since vast numbers of abortions have been performed in free-standing centers. There is no measurable increase in risk because of multiparity, previous cesarean sections, previous cardiac surgery, or well-controlled diabetes, epilepsy, asthma, etc. The medical eligibility decision is based on the state of the woman as she is examined at the time of the abortion.

The next important consideration is the reception of the woman at the facility. Every effort was made to make the reception and waiting areas at PRETERM as warm and inviting as possible. They are constructed along the lines of a comfortable hotel waiting area and not on that of a stark, modern hospital clinic. The atmosphere is one of quiet and courtesy. The receptionists have been trained to allay anxiety and to facilitate the initial registration procedures that are necessary to develop a patient record. Laboratory work is minimal. However, each patient has an examination to determine that day whether or not she has a positive pregnancy test and has either protein or glucose in her urine. In addition she must have a blood hematocrit and Rh typing. The patient may then have a pelvic examination if there is some question as to the duration of the gestation, or she may proceed directly to counseling.

Abortion counseling is unique in that it provides the opportunity for a woman to spend an adequate amount of time to clearly determine the alternatives available to her for this pregnancy. She is allowed sufficient time to weigh these alternates, to clarify her life situation, and to make the decision by herself, free from any elements of pressure that may have been imposed upon her by people in her home environment. No pressure is exerted to push her into a decision she cannot live with. The atmosphere during the interview is one of empathy and understanding. The women who have been trained as counselors have been very carefully screened so that no judgmental factors appear during the actual interview. The abortion counselors have been recruited from many sources, but their outstanding characteristic is their ability to relate to other human beings in crisis. When the decision has been made whether or not to have an abortion, the conversation may proceed to informational matters, although these may occasionally have been given in a small group prior to the one-to-one counseling process. The informational matters center around the technical occurrences of the day: what it is like to have an abortion under local anesthesia, and what one can expect during and after the procedure. In addition the woman's contraceptive and reproductive knowledge is explored. She is given the opportunity to select a contraceptive that she feels she can manage and then is given sufficient information so that one could reasonably expect her to be able to use this contraceptive method.

Following the interview the woman is brought to a procedure room which is painted in a restful color and is as free of extraneous and anxiety-producing equipment as is possible. An ordinary examining table is used. The woman is instructed to remove her undergarments, but no further undressing is required. A simple underpad is placed beneath her and a paper drape over her lap. No further draping and no other sterile environment is provided. The surgeon uses a "no-touch" technique which is reminiscent of the way one does endometrial biopsies in the office, though astounding to those who have always done surgical procedures with full draping, "prepping," and use of sterile linens.

After a careful bimanual examination and visualization of the cervix, the vagina is cleansed with a small amount of povodine-iodine solution. The cervix is infiltrated at twelve o'clock with a small amount of 1% Carbocaine; a single-tooth tenaculum is then applied at twelve o'clock using a deep vertical bite that goes through the cervical os. The remaining paracervical block will then be given, usually at four sites (3, 5, 7, and 9 o'clock), using 3–5 ml of the anesthetic at each point. After waiting several minutes for the block to take effect, the cervix is gradually and gently dilated using Pratt dilators. A suitable sized vacuum cannula, either flexible or rigid, then is inserted and the contents of the uterus carefully aspirated. During the period of aspiration, strong uterine contractions may occur. The counselor is present to reassure the woman and advise her that the end of the procedure is near. Only rarely is it necessary to give a systemic analgesic for this procedure. Following the emptying of the cavity with the suction curette, a sharp curette is used to check the completion of the abortion. This is particularly important when the uterus is angulated. The cavity is then re-aspirated for 10–15 seconds to remove any loose decidua, an IUD inserted if desired, and the equipment removed. The operator then carefully reviews the tissue obtained to be sure that (1) the patient was pregnant, (2) he did in fact complete the abortion, and (3) all fetal parts are present. At this time it may be noted that there was insufficient tissue obtained even to be sure if the patient was pregnant, and other problems that occur during the performance of an abortion may be discovered.

Following the termination of the pregnancy, the counselor who has been present, supporting the patient throughout the procedure, accompanies her to the recovery room, where she is encouraged to sit in a comfortable chair (or occasionally to lie down on a couch if necessary) for at least an hour. During this time light refreshments are served, her post-abortal instructions are reviewed, and she is given a booklet to take home that will cover all of these points. Oral contraceptives may be provided at this time, and group discussions take place to acquaint her with the possible problems of the post-abortal state, to remind her of the technique of using contraceptives, and generally to reassure her that she is not unique and that other women have required an abortion. During the time of her follow-up visit, additional opportunities are given to her to resolve any persistent feelings relating to the abortion that may be troubling her.

The efficacy of first trimester abortions in free-standing centers has gradually been demonstrated over the last three years. It is clear from a review of the efficacy and safety records of the nonprofit centers that first trimester abortion is a safe medical procedure. While the risks are somewhat greater than those of contraception, they are far lower than term pregnancy. Further, the opportunity for women to acquire contraceptive knowledge and to be taught and given a modern contraceptive is such that the necessity for repeat abortions is diminished so that in the future hopefully abortion will be needed principally for contraceptive failures.

Summary and Conclusions

The author has reviewed the efforts made during the last two decades that have culminated in the Supreme Court decision that made abortion available to women of the United States. This decision has assured women of the right to make decisions regarding their reproductive life without the necessity of outside interference. The last three or four years have resulted in the establishment of the free-standing center which enables women to have an abortion on an ambulatory basis during a period of several hours and at low cost. A description of the services provided at PRETERM Washington is given. Concepts of providing a humane and empathetic service using extensive counseling to help the medical decision-making and to provide information regarding the abortion service and contraception are unique. The performance of abortions under local anesthesia using a vacuum aspirator is also described. It has been shown that first trimester abortion is a relatively safe medical procedure and that a consistently high-quality, humane service can be provided at reasonable cost.

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Therapeutic Listening: An Adolescent Guidance Program in Motivation for Contraception

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The problems of sexual ignorance and failure of psychosexual maturation have been reflected in rising rates of out-of-wedlock pregnancy in our clinic as well as in the nation. There has been a clear need for the study of these problems, and also the study of decompensation of interpersonal relations in marriage so frequent in our society. The response of physicians to these problems has been poor, for neither gynecologists, nor psychiatrists interested in sexual malfunction, nor family planners, nor sociologists interested in marriage problems had come together in a meaningful way to explore patient care, research, and educational channels in this difficult area.

Clearly an interdisciplinary team would be required to study psychosexual phenomena in adolescence, motivation for contraception, psychoemotional reactions to reproductive physiology, and interpersonal relations in young married groups to provide a firm data base for any family health type of activity.

The development of comprehensive programs to meet the needs of pregnant adolescents living at home is a recent trend, and the 1960's saw the establishment of many such programs. However, the rising illegitimacy rate among adolescents suggested that service programs alone did not answer the needs of these adolescents. Our department always has identified the adolescent out-of-wedlock patient as a high risk obstetric patient with multiple social and psychological problems. In 1966, we initiated a multidisciplinary Adolescent Guidance Clinic at Mount Sinai to conduct research into the motivation for contraception and pregnancy in this population, and to analyze data for the development of a family life program for service to the community and education of undergraduate and graduate physicians.

The clinic is concerned with the health of a ghetto area, East Harlem, where medical care is barely adequate for some and preventive medicine meager for all. The provision of specific assistance with the physical, emotional, and social problems of the sexually active adolescent can make a significant contribution to the welfare of such a group and serve as a model for other communities. Our clinic may be unique in its interdisciplinary study of adolescents and their families while providing medical care and counseling for pregnant out-of-wedlock adolescents aged sixteen and under. By age seventeen, most females have reached biologic maturity. Pregnancy for the married adolescent in this young adult

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group carries no greater risk than in the twenty to twenty-nine year age group. However, out-of-wedlock pregnancies, regardless of age, carry a higher risk. The major goals of the clinic are to provide:

1. Methodology experience to be used in the development of a core curriculum in adolescent sex education and marriage counseling for undergraduate and graduate students.
2. Study of the motivation, techniques, and special services effective in the dissemination and acceptance of contraception.
3. Accumulation of data regarding motivation for contraception or pregnancy on the basis of psychological testing, psychiatric interviews, social and cultural milieu, and social pathology.
4. Coordination of gynecologic and obstetric care with the adolescent medical program.
5. Coordination of care by the same professional group before, during, and after delivery for patients who were carried to term.

For this effort, a multidisciplinary team from the Departments of Obstetrics and Gynecology, Community Medicine, Psychiatry and Social Service was developed. With funding from the Rockefeller Foundation, this team investigated over four hundred adolescent out-of-wedlock pregnancies, the complex interaction involved in their causation, and methods for the prevention of recurrence. The team consisted of social service workers, a public health nurse (later a nurse-midwife), a psychiatrist, a psychologist, and the obstetric staff, all under the direction of an obstetrician-gynecologist with public health training.

Study areas. Since the traditional randomized clinical trial was not possible in this complex psychobiologic system, it was necessary to establish "comparison" groups to study the various aspects of social, psychiatric, and motivational factors that result in teen-age pregnancy. Already available at Mount Sinai were the following groups:

1. Adolescent unwed mothers electing to continue their pregnancy—Adolescent Guidance Clinic
2. Adolescent unwed mothers electing to terminate their pregnancy—Voluntary Interruption of Pregnancy (VIP) Service
3. Adolescents who voluntarily seek contraceptive advice—MIC/Family Planning Project.

Each of the disciplines involved in the project undertook to develop methodology that would allow for systematic collection and codification of data so that variable control could be attempted. In most cases, service and research were intimately intertwined.

Intellectual and personality evaluation. The focus of psychological research started with intellectual and personality evaluation. The major goal was to arrive at an assessment of the patient population in terms of intellectual capacity and personality development. Such data could provide us with information regarding motivation within this population leading to pregnancy.

The goal was pursued through the use of a battery of standard psychological instruments, specifically the Wechsler Intelligence Scales, the Thematic Apperception Test and the Rorschach Ink-Blot Test. It was demonstrated, through data collected via these instruments, that problems of intelligence did not appear to play a significant role in the occurrence of these pregnancies. The intelligence quotients for a sample of the population displayed a normal distribution with a mean of 86.2 and a standard deviation of 11.9. There was no statistically significant difference between the Puerto Rican subsample (82.6) and the Black subsample (88.8). The above means, which are below the average of the standardization group, reflect social, cultural, and educational differences and are only approximate measures of intelligence. This has been noted in other studies of similar socioeconomic groups.

Personality testing in this sample resulted in the clinical findings that dependency needs, oral aggression, and a sense of damage and/or incompleteness, while typical of adolescence, were the sources of greater conflict for the deliverers and aborters than the contraceptors. It was concluded that while dependency conflicts, along with lack of self-esteem, appeared to be very common in our population, these characteristics were not sufficient explanations for the action resulting in pregnancy. Further analysis of this data will be presented in a later report.

More specific information regarding the multiple forces at work within our population was required. To this end, it was decided to develop instruments which would provide more specific information about the experience of pregnancy and sex, its meaning, consequences, and determinants. The following two instruments were added to our data-collecting procedures.

The Adolescent Guidance Questionnaire: This instrument is a self-administered questionnaire composed of sixty-one questions. The questions are in closed form, i.e., alternative answers are provided which the subject checks.

The items in the questionnaire cover several major areas: a. nature and duration of the relationship between the girl, her boy friend, and peers; b. knowledge and attitudes about contraception; c. knowledge and attitudes about sex; and d. parental influence on sexual and contraceptive behavior. The questionnaire is seen as a source of information about each girl's conscious picture of herself in relation to these areas. Several trends emerge from some of the collected data. Most of the girls spent the majority of their time with girl friends. They were not promiscuous although they were sexually active with a particular consort. Pleasures other than genital appear to constitute a major source of motivation for sexual intercourse. Knowledge of reproductive functions was minimal and availability of this information in the home was lacking. While most were knowledgeable about contraceptives, misconceptions and ignorance about the facts of birth control colored their attitudes toward using such methods. In addition, there was a general lack of knowledge about where to obtain effective contraception. A number of cognitive and attitudinal forces appear to have been at work determining the non-use of contraceptives by these girls, and a combination of ignorance about sexual and contraceptive matters and a lack of accessibility to birth control methods was found to be a significant force in this regard.

In the comparison groups, teenagers within the same age range who elected to have an abortion have been included. Comparison of this group's responses with those from the group who will continue their pregnancies indicate certain differences. The questionnaire was also administered in a school setting to a group of boys and girls of similar age. These data are now undergoing analysis.

The Pregnancy Apperception Test: The Pregnancy Apperception Test (PAT) is a projective test designed to explore the experience of pregnancy. It consists of ten cards, each depicting a scene involving a pregnant girl or girls in different situations. The cards include drawings of a girl with a teacher, with a mother figure, with a father figure, with nonpregnant peers, with pregnant peers, with a boy, with a doctor, with a doctor and a nurse, by herself, and with her baby. The girls are instructed to make up a story for each card, and their spontaneous remarks are recorded. The test provides information about certain specific areas. If these areas are not covered in a girl's spontaneous response to the cards, then certain predetermined questions are asked. Through the PAT, information about the girl's reaction to her pregnancy, her significant relationships, her response to these effects, her acceptance of pregnancy and the child, and other pregnancy-related phenomena are studied.

Response categories have been developed as a way of standardizing the answers. This is part of a validating process being pursued for the test. It is hoped that this test may be used as a screening method for early identification of patients prone to psychiatric problems, poorly motivated for contraception, and at high risk for recidivism. The PAT also has been administered to an abortion group. Responses will be compared, with the intention of identifying differences between these groups in regard to the above factors. The psychiatric interview and psychological test procedures were coordinated so that specific information was gathered through two different, independent techniques.

Standardized psychiatric interview. A structured, in depth, standardized psychiatric interview has been developed which is being used to evaluate the intrapsychic and environmental factors which might predispose an adolescent toward having an out-of-wedlock pregnancy. Specific questions and issues to be clarified regarding these patients came from the clinical case material and clinical experience of each team member. The data about each patient are accumulated in a retrievable fashion so that they may be correlated with that of the other disciplines. This approach may also help us identify the factors involved in recidivism.

Social Service. In reviewing Social Service contacts with patients and their families, it was found that there were specific areas which could be identified for additional service, research, and teaching. These areas have been incorporated in the Social Service Questionnaire, which was developed on the basis of problems uncovered during the course of prenatal and postpartum care of the study group. Initially, the outline was used to examine more closely the concerns of this patient group and to evaluate the extent to which we were able to deal with these problems. During that phase, it was discovered that the outline could also be used as a tool for collecting data. It is designed to give a descriptive, personal, social analysis of the patient and parent or guardian. Since almost all of these patients live at home with a parent or guardian, one must work with those individuals who are most influential in the patients' lives. The outline traces the process of contacts with the patient and her family from the prenatal through the postpartum period, and shows at a glance the areas which require intensive care in helping the patient plan for herself and child.

Many of the study group patients and their parents lack adequate knowledge of health, hygiene, sex, and contraception. For some, their own life situation brings negative feelings when these subjects are introduced. In these cases, parents and/or patients' feelings of embarrassment might be greater than lack of knowledge. Thus, in addition to providing information, they must be helped to deal with these feelings in order that they might make adequate use of a contraceptive method.

Summary and Conclusion

The aim of this project is to use the methodology developed in the interdisciplinary Adolescent Guidance Clinic to establish a program of research into the prevention of pregnancy in unwed adolescents, and to translate this data into a marital health clinic for service and research in the sociologic, cultural, psychologic, and physical problems of conception control. This resource will be utilized further for the instruction of undergraduate students and graduate physicians in family life and family health, with special reference to the indigent community that our clinics serve.

This will be accomplished first by studying the social, psychiatric and motivational relationships in the comparison groups: a. Adolescent unwed mothers electing to continue their pregnancy; b. Adolescent unwed mothers electing to terminate their pregnancy; c. Adolescents who voluntarily seek contraceptive advice. Using our protocol of psychiatric and psychological examination and testing, differences in the motivation of these separate groups can be determined.

Secondly, the knowledge already obtained has been used to develop public school-based programs of education in sexual physiology and family life, with emphasis on the prevention of adolescent pregnancy. This experience will also be used in establishing courses of instruction for physicians, medical students, and allied health personnel. Using modern methods of data processing, there will be a continuing analysis of the motivational study. Information from this analysis will then be used to modify the educational programs on an ongoing basis.

The forementioned groups presented a unique opportunity to study many aspects of the social, psychiatric, intellectual, and educational factors that enter into teen-age pregnancy. Further subdivision of the groups on the basis of demographic data allowed for more specific analyses. Essential to this was the development of a record system for initial and continued data collection. The study methods developed by the program were coded, keypunched, and computer-analyzed. Collection of the data was a team effort by gynecologists, an adolescent psychiatrist, a psychologist, and social workers. By this epidemiologic approach, we have obtained answers to a multitude of questions involving knowledge, attitude, and practice of contraception. Furthermore, in conjunction with part two of the project, the effect of available education and contraceptive methods on these subjects can be ascertained.

Our project to date has permitted us to develop a technology suited to the evaluation of motivation for contraception and to utilize some of the data in our care of troubled, deprived adolescents and their families. In addition, with the development of this study team and an operative focus for problems of sexual development and maturation, we have started a significant educational progam for undergraduate and graduate physicians in this area of great need and small knowledge.

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Alan F. Guttmacher, M.D.: His Role in Teaching Human Sexuality

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Dr. Guttmacher played an influential role in sex education, especially during his tenure as President of Planned Parenthood Federation of America, Inc. His absorbing interest for most of his life was in family planning and birth control control education, a more limited point of view than he took later in life. Education in contraceptive techniques and the anatomy and physiology of reproduction took center stage in his teaching until the 1960's, when he became more interested in the psychology and sociology of sex. Indeed, it is a testimony to his versatility and flexibility that relatively late in life he became deeply concerned about the sexual attitudes and values of young people and through lectures and books tried to reach them with his ideas.

One of Alan Guttmacher's great loves was teaching. His skills as a teacher of medical students, interns, and residents are well known. He was a superb teacher, having great fluency of language as well as great depth of knowledge and understanding about his specialty, Obstetrics and Gynecology, and later his particular area of interest, fertility regulation. In addition to the standard subjects of his specialty, he became known for his teaching of special subjects such as birth control, abortion, and sterilization. He displayed a great gift for openness and frankness, so that the so-called "controversial topics" like birth control and abortion would be thoroughly discussed with his students. To add life and human interest to his teaching, these subjects were always related to the human situation. For example, Dr. Guttmacher never hesitated to illustrate a point by describing the plight of a low-income woman with an unwanted pregnancy, unable to obtain an abortion because she could not afford the fee.

By the time that he assumed the presidency of Planned Parenthood in 1962, he already had established a reputation as an educator in the family planning field, publishing *The Complete Book of Birth Control* (1) and *Planning Your Family* (2). These were but the beginning of a plethora of publications, both for the professional and lay public, on birth control and related subjects.

One of Dr. Guttmacher's main roles as President of Planned Parenthood was that of a "missionary," to make acceptable the idea of birth control, responsible parenthood, and wanted children. Probably one of his greatest contributions as an educator about human sexuality was his ability to speak effectively before professional and lay audiences about his favorite topics. Because of his erudition and charisma, he was able to give thought-provoking lectures which openly discussed sexuality and reproduction, including the anatomic and physiologic terms appropriate to the subject. Thus, in the early 1960's, it was not uncommon to hear Dr. Guttmacher frankly discussing birth control methods in which he

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freely used terms such as "penis," "vagina," "orgasm," and "sexual frustration" —at that time still shocking to many people.

By talking frankly and openly as he did, Dr. Guttmacher did much to break down taboos. He recognized the impact of audio-visual materials and became involved in developing films. One of the early ones, designed for professional audiences, was entitled "Fertility Control and the Physician"; it undoubtedly did much to educate physicians and nurses about sexual function and human reproduction.

Dr. Guttmacher humorously referred to his expertise in discussing the Jewish attitude toward birth control, as well as toward reproduction and sexuality. While he made light of his skill, many felt that his excellence in discussing Jewish attitudes and beliefs often managed to provoke an examination of other religious attitudes toward these important topics. From this it was a short step to a discussion of societal and cultural attitudes toward sex, reproduction, and birth control. Again, Dr. Guttmacher had the gift of being a proselytizer about responsible sexuality and parenthood.

By the mid-1960's Dr. Guttmacher had become a popular speaker on campuses, both for faculty and students. For example, in late 1966, he met with the faculty of Francis Parker School in Chicago and then with individual teachers the following day. Parker was evolving its own program of sex instruction, and sought Dr. Guttmacher's advice in putting this into more concrete form. At around the same time, he met a class of Barnard College first-year students. As reported in the *President's Letter* (No. 18, December 28, 1966) (3), the pertinent facts about the physiology of human reproduction, the history of conception control, and modern methods of limiting family size, were discussed. Dr. Guttmacher further reported that he stressed the importance of personal responsibility in sex relationships. At Barnard, he answered the questions the girls had submitted in writing. On both occasions, he reported a frank and free discussion of sex on the modern campus. Some of the questions submitted to Dr. Guttmacher are interesting. Here is a sample:

> "If a student wants information about contraceptives, where can she get it?"
> "Does Planned Parenthood prescribe contraceptives for unmarried girls?"
> "Please specify the requirements for getting them through your organization."
> "If a student living away from home believes that she may be pregnant, what should she do?"
> "Please explain the rhythm method in detail."
> "Are there any harmful side-effects to contraceptive pills?"
> "If legal abortion doesn't solve the problem of illegal abortion, what will?"

This was just an example of one of many experiences Dr. Guttmacher had in speaking before faculty and/or student audiences. One cannot help noting that all questions he chose to report were on contraception, pregnancy, and abortion. Questions about premarital sex, masturbation, and about personal relationships were omitted; and it was not until the end of the 1960's that he realized that he ought to put his ideas about those subjects in print, which he did in a book entitled *Understanding Sex: A Young Person's Guide* (4).

During 1966, Dr. Guttmacher attended the Princeton Conference on Sex Education, held under the auspices of the National Association of Independent Schools. As a result of this experience, he received other invitations such as one to Wellesley College in Massachusetts. There Dr. Guttmacher held two 2-hour sessions with each class, discussing the need for sexual responsibility in this era of changing and conflicting sexual mores. He met with the faculty, and also addressed the annual meeting of the parent-teacher association of the school. Dr. Guttmacher noted that when he shared with the parents some of the searching, frank, and intelligent questions which the students had put to him, their complacency was "rocked." Dr. Guttmacher often expressed his admiration for the younger generation; he felt that they were concerned with real social issues, had a healthy attitude toward sex, and had the possibility of developing into finer, better-balanced Americans than their parents.

Dr. Guttmacher was aware that his age might hinder him from really reaching students. However, there seemed to be excellent rapport when he spoke before college audiences. For example in 1967, when he spoke before one college audience on "Sex Mores on the Campus", he was asked the following question: "Doctor, I think you have a poor case for marriage. It is an outmoded institution. Why shouldn't we junk it?" Another student questioned Dr. Guttmacher's belief that, if one is going to practice premarital sex, fidelity in premarital relationships was very important. (Dr. Guttmacher advocated serial monogamy rather than promiscuity.) The student opposed Dr. Guttmacher, defending maximum promiscuous premarital sexual experimentation. Dr. Guttmacher tried to answer both challenges, but was not certain that he won the debate in either instance. He reported, however, when he answered one of the girl's questions, "What advice would you give a woman who never intends to marry?" that he evoked howls of laughter when he gave the answer: "Don't die a virgin." He noted that perhaps students might not classify him as a complete "square" after all.

This leads to some description of Dr. Guttmacher's interest in outlining a code of sexual responsibility. In February, 1967, he visited several New England campuses as the Billings Lecturer of the Unitarian-Universalist Church. His subject was: "Sex Mores on Today's Campus," a title which had been selected by his sponsors. He lectured at the University of Massachusetts, the University of Connecticut, Springfield College, American International College, Hartford College, Trinity College, Yale Divinity School, and Yale College. In his presentation, he presented a code of sexual responsibility. Here is a quote from the summary of his discussion, as presented in the *President's Letter* (No. 3, August. 1967) (5).

> Since today's youth is governed by a single sex standard, not the old familiar double standard of the past, my advice applied equally to men and women. I made four points. First, for many, probably most, premarital sexual intercourse is likely to be an unsatisfactory, far from wholesome experience. This would be particularly true for those who come from conservative homes with highly structured ethical backgrounds in which religion plays a

> significant role. This is the group most likely to develop a strong guilt reaction and recriminations. On the other hand, for some from more permissive homes and for others in actual revolt against home and church, premarital sex might be justified and right, if it grows from a deep and meaningful relationship. I stressed that premarital sex should be initiated only after deep and sober thought. I tried to make each student realize that he and he alone can make so important a personal decision. Before marriage no one owes sex to anyone else. Second, exploitation of a sexual partner by threat, bribe, or coercion is grossly immoral. I had in mind particularly those partners who seek to induce another to participate on the grounds that "everybody does it," or that he or she will cease dating unless intercourse is agreed to. If premarital intercourse is to take place, it is dead wrong unless the participants are mutually enthusiastic. Third, sexual promiscuity is just as wrong before marriage as it is within marriage. And in one sense, actually more evil, since it could establish a pattern of promiscuity for marriage. Fourth, all sexual intercourse outside of marriage must be protected by effective contraception. Failure to use birth control, I told them, is the grossest form of sexual immorality and irresponsibility, because it may lead to the tragedy of an unwanted pregnancy which involves both parties, the innocent conceptus, and more than likely the couple's parents as well. All solutions to such a situation leave deep wounds —whether it is forced marriage; illegal, clandestine, dangerous abortion; a fatherless baby: or a child surrendered for adoption. Even the Yale Divinity students, judging by their sustained applause, found the code I presented satisfactory. At Yale, as I inveighed against premarital promiscuity, I said: "I have little respect for the man who flits from flower to flower." Then I paused, groping for a suitable floral appellation for women. And I continued: " . . . or the girl who ventures from thistle to thistle." My unplanned *bon mot* brought down the house.

It is clear that Dr. Guttmacher, by this time, was becoming deeply involved in the discussion of attitudes and values related to sex. This culminated in his writing the book *Understanding Sex: A Young Person's Guide*, mentioned earlier. The quotation from the *President's Letter*, cited above, is fairly explicit evidence of Dr. Guttmacher's essentially conservative values with regard to premarital sexual intercourse. Although he recognized that values were the primary concern of young people and that sexual choices and decisions were at least as important as fears of pregnancy, or ignorance about contraceptive methods (indeed, he noted that these values usually shaped *contraceptive* as well as sexual behavior), he devoted only two of the eleven chapters in the book to the psychological and social aspects of teenage sexuality. The other chapters were biomedical in content.

Guttmacher believed that sex has little meaning, and is often harmful, unless it is accompanied by loving feelings. Thus, Guttmacher said:

> To be sure, sexual intercourse can and does take place on many occasions and with many people without love: for example, the prostitute who sells her body or the couple who sleep with each other after slight acquaintance and without any deep emotional involvement. Then the sex act has a different meaning; it is bereft of love and is simply a mechanism for the release of sexual tension . . . (but there is nothing inherently evil in premarital intercourse) . . . I cannot say that it is absolutely wrong for everyone (6).

Guttmacher gave the impression that under unusual circumstances premarital sexual intercourse may be a meaningful growth experience of the two people, but that in most instances, it is a mistake and potentially harmful. He expressed the view that if two people are living harmoniously with one another, their sexual relations almost inevitably are also satisfactory. Most marriage counselors would probably disagree with this statement, since they have clinical evidence that some relationships otherwise harmonious and gratifying, can be deeply troubled by sexual problems. On the other hand, most sex educators would probably agree that Guttmacher's viewpoint is essentially correct in linking satisfactory marital relationships with sexual relationships, although he did not allow enough latitude for the broad range of sexual experience.

Even if Dr. Guttmacher comes across as being somewhat more conservative than most contemporary sex educators, his major message about the need for responsible relationships, including contraceptive responsibility, and his inveighing against sexual exploitation and the misuse of sex were important messages to have been delivered to young people, and are as valid today as they were when delivered.

Indeed, Dr. Guttmacher's essential conservatism and his preaching of sexual responsibility put him in great demand on college campuses. It is likely that many more people were influenced by his ideas than by people they may have regarded as being "too radical." Knowing his conservative value position with regard to premarital intercourse, many people were more easily persuaded with regard to his views about abortion and sterilization.

He continued his demanding lecture schedule, and became more and more involved in discussions on campus. He always talked birth control, responsible parenthood, and the need for wanted children. He became more and more involved in discussions of the burning question of population growth and its implications. One of the most important functions he served was to influence physicians in charge of student health services. It was at this time that his discussions about human sexuality became more practical. His great powers of persuasion undoubtedly made it possible for many college officials to begin considering making available contraceptive and counseling services on college campuses. It should be noted that Planned Parenthood Federation developed a college program specifically to work with college students and faculty. Dr. Guttmacher was enthusiastic about this special program within Planned Parenthood and supported it energetically.

During the 1960's, Planned Parenthood affiliates forged ahead and developed their own programs of education in human sexuality. Many of them were ahead of Planned Parenthood Federation itself in advocating the integration of sex education into the educational programs of family planning agencies. One of the authors, Dr. George Langmyhr, during his tenure as Medical Director of Planned Parenthood Federation, 1967–1972, was well aware of the many requests made to the Federation for more leadership in the field of sex education.

It is not clear how Dr. Guttmacher felt about the institutionalization of sex education within the Planned Parenthood program. Perhaps he may have had some reluctance to make education in human sexuality a significant part of his agency's program because of his fear that Planned Parenthood would be smeared with the same tar brush that right wing extremists had used against SIECUS (The Sex Information and Education Council of the United States). It is also possible that he may have wanted to avoid competing with SIECUS. There is some confirmation of this through noting that after the National Medical Committee of Planned Parenthood requested some discussion of the Federation's possible role in Sex Education, a meeting was held with representatives from SIECUS, various Planned Parenthood Federation affiliates, and certain Planned Parenthood staff. Dr. Guttmacher noted SIECUS' role, and the need to avoid conflicting with that agency's program. However, Dr. Mary Calderone, Executive Director of SIECUS, because of her strong conviction that sex and contraceptive behavior have to be considered together, saw a need for Planned Parenthood to become more involved in sex education. Furthermore, she, like others, felt that the affiliates could play a very significant role in developing community sex education programs. The affiliates' obvious community involvement through their service programs could lead to an extension of sex education programs. The meeting ended inconclusively, particularly when Dr. Guttmacher noted that the Federation was having financial problems and probably could not expand and develop a separate program in human sexuality education. One of the side-effects of this meeting was the development of a grant which led to a specific training program by Marriage Council of Philadelphia in 1972 74, to which eighteen affiliates of Planned Parenthood sent staff members to be trained in human sexuality and sex education.

The various influences on Dr. Guttmacher's attitude toward sex education can be summarized:

(1) his strong biomedical orientation as a physician and medical teacher;
(2) his decision to give priority to contraceptive education rather than to sex education, in the wider sense of the term;
(3) his strong interest in abortion reform as a more practical way of reducing the number of unwanted children, as well as the horrendous effects of illegal abortion;
(4) his conservative value system, which made him approach sex education cautiously; and
(5) his flexibility, which made him respond to young people's needs as he heard them during his wide ranging discussions with college youth.

As a marvelous teacher—erudite, articulate, persuasive—had he lived a few years longer, he would have played an increasingly important and active role in many different aspects of sex education. Within the narrower range of contraceptive, abortion, and sterilization education, his influence on the profession, the laity, and on important decision-making bodies of government was profound.

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The Need for Comprehensive Programs for School-Age Parents

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In his last few years Alan Guttmacher was, in the eyes of many, Planned Parenthood. Thus it is not surprising that as the issues identified with Planned Parenthood engendered more and more emotional response from critics, he became the focal point of attacks on birth control and abortion. Yet this great physician had equal concern that all who wanted children should have them, and that these children should be healthy. He came from a family distinguished by its interest in people and their welfare. It is therefore fitting that an article honoring him advocate comprehensive services for school-age parents, especially since the specific program described was organized under the auspices of a Planned Parenthood affiliate.

There are many programs in the country which are designed to help the schoolgirl who becomes pregnant, yet all but three or four are organized around one or two specialized services, with the result that other areas are often neglected. For example, a program organized within a school system may offer excellent instruction to those who attend the school while offering little help to those who attend irregularly, who need special health services or social counseling, or who are in trouble with law enforcement authorities. It is difficult for a young girl to keep up with her school work when she must take time out to receive medical care, or when her family or friends do not offer her emotional support, or if she is concerned about whether she should keep her baby or offer it for adoption, or how she can mobilize financial support, or how she will learn to care for her baby, or if not married should she get married. She falls behind academically and may well drop out, most likely with the school staff unaware of the pregnancy. Even if aware of all that is taking place, the schools do not have the resources to see that all needs of the girl are cared for, especially in competition with other students who have special educational requirements.

Recognizing the difficulties in arranging for all services needed by the pregnant teenager, a group of Tulsans representing the local Planned Parenthood affiliate, the health department, and other community agencies organized, in 1970, the Margaret Hudson Program for School-Age Parents. This was called a "program" rather than "school" to emphasize its comprehensive nature, and named in honor of a public health physician who was an early advocate for improved maternal

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and child health. Policy was established by a board composed of representatives of 20 cooperating agencies, the students, their parents, and the community at large. The program has been restricted to those enrolled in school and under the obstetric care of a private physician or a public clinic. Each girl remains on the roll of her home school while attending classes and receiving other services at the program headquarters. The school board has furnished a surplus school building. Approximately six weeks after delivery, the girl returns to her home school, and follow-up services are continued by the program. Girls preferring to remain in their home school may do so. The program opened with an enrollment of 30 and a coordinating staff of a director, a secretary, and a part-time administrative assistant. All other services were provided by volunteers or by cooperating agencies. Within two months, a long waiting list showed a gross underestimation of the number of pregnancies among school girls.

Since its incorporation, the staff has grown to 20 full-time and more than 40 part-time persons; more than 1,000 individual students have been served. The maximum at any one time is 90, and a summer program has been included on a regular basis. From the start, efforts have been made to avoid duplication of services and facilities and the program has served not only as a coordinating agency, but has been an important influence in developing communication and cooperation in general among various agencies in the community. Among the services furnished within the program are classroom study, health education, auxiliary nursing services, teaching of leisure skills, vocational counseling, teaching of arts and crafts, social counseling and follow-up and, at times, transportation. Among services obtained by referral are homebound study when appropriate, adoption services, and financial assistance. No domiciliary services are furnished, though there is close cooperation with other agencies which do provide such services.

From the beginning, each professional component has been responsible for the standards in its area on the premise that educators know best how to teach, health professionals how to deliver health care, and mental health, support, and social work counselors how to give counseling. As a result, for instance, all teachers must meet the standards and be approved by the schools and credit for courses completed is not jeopardized. Students range from the affluent to the poor.

Financing has been a problem, with the major support coming from federal sources, Model Cities, LEAA and YDDPA*, and city-county revenue sharing. Presently efforts are being made to secure funding from state sources. Efforts to secure private funding, including the United Way, have brought many small but no large contributions.

Has the comprehensive nature of the program been worth the extra cost, estimated at about $800 per student, if judged solely on a dollar basis? We think so. Although the nature of school-age pregnancy makes statistics difficult to collect, we have an enviable retention rate for this very high-risk group. A 1972 study of 119 students who should by then have completed high school found that 84, or 71 percent, had done so. The holding power in 1970–71 was 94 percent. In one year's time, the repeat pregnancy rate was reduced from 25 percent to 15 percent. When one considers that unemployment and underemployment have been reduced, tax-paying has increased, and welfare payments been reduced, there is no question of recovery of the dollars spent on the program.

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* LEAA, Law Enforcement Assistance Act, Department of Justice; YDDPA, Youth Development and Delinquency Prevention Administration, HEW.

What about the quality of life for the students? Students uniformly develop an enhanced sense of goal direction and learn to use their increased knowledge, including how to use health and social service resources. A study reported in 1973 by Doggett* noted in these students a high level of alienation, indicating a distrust of and estrangement toward others. There was improvement in this trait, as well as in social maturity and adjustment. Despite considerable improvement during the several months in the program, it is evident that even more time is needed to reverse all the problems resulting from many years of having to cope with broken homes, poverty, and alienation from society, especially for the group already involved with the juvenile courts. It is of significance that during the follow-up period, and even afterwards, the girls seek help from the counselors.

In addition to the benefits received by the girls themselves, considerable help has been given to their families and their friends. There is no way to determine the number of pregnancies prevented in younger siblings and friends through change of attitudes, but the number must be significant. Likewise we cannot determine the full impact on the improved relationships in the homes of the girls.

One help to the community has been the bringing into the open the problems associated with school-age pregnancy. The fact that one girl in ten was having at least one child before age 18, or graduation from high school, has startled even some of the professionals working with the girls. This excludes girls whose pregnancies have been terminated.

There is also a growing recognition that married school girls and their families, almost as much as the unmarried, need help to adjust to the many problems they encounter. The pressures for both the girl and her husband to drop out of school are great. The husband is likely to be underemployed for the rest of his life unless help is given him. The high divorce rate in this country is greatly accelerated if marriage occurs in the teens.

As the program has developed, we have recognized the need for alternative educational goals. Whereas some students properly should continue toward the baccalaureate programs, others should shift to a junior college program, and some to vocational technical schools. For some, efforts should be placed primarily on teaching "survival skills" with an intent on reaching the diploma stage. Also it must be recognized that while some students can carry enough credits to graduate on schedule, this is not always practical. There is an advantage in keeping up some classes rather than dropping out, for then the break in education that might make starting back difficult does not occur.

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* Doggett, J. C., Ph.D.: An Evaluation of Certain Attitudes, Knowledge, and Change in Pregnant Adolescents Attending The Margaret Hudson Program (From a study for the Tulsa City Demonstration Agency, Feb. 1973).

In two areas we are deficient in reaching our goal of comprehensive services. Both are projected for the future when sufficient funding can be mobilized. One is a day care center to use as a laboratory to improve the teaching of parental skills, and the other is a program aimed to a greater extent at young fathers and at educating those in the community prior to their becoming parents.

Summary

Without the development of a comprehensive program, neither school-age parents nor the professionals helping them can easily mobilize the total resources of the community necessary to prevent such problems as broken homes, under-employment, repeated unwanted pregnancies, school dropout, and delinquency. The program itself tends to make the community aware of the problems and acts as a stimulus to the development of healthy attitudes of children and adults towards responsibility in areas of sexuality as in other areas. School-age parentage is not solely a school problem, a health problem, a social welfare problem, a family problem, or a personal problem, but a community problem.

Psychosocial Aspects of Abortion in the United States

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Elective abortion has become an option for large numbers of women in the United States only recently, as a result of legislative changes in the late 1960's and early 1970's and by virtue the 1973 Supreme Court decisions. Of necessity, early research on abortion focused on small groups of women who had been granted therapeutic abortions under restrictive conditions or who had procured illegal abortions on their own in the United States or in other countries. During the past several years it has become possible to study larger numbers of women, to establish baseline demographic data, and to explore some of the more complex factors related to abortion. In recent studies, information has been obtained concerning patient motivation, impact of the procedure at different periods of gestation, and differences between first and second trimester abortion patients.

We will review some of the literature concerning the psychological effects of abortion both before and after legalization and will share the results of our own research, first briefly summarizing the results of a program during the implementation of liberalized abortion in New York State, and then presenting data from a program in Pennsylvania. An exhaustive review of the literature will not be attempted; the interested reader is referred to several good review articles which have appeared in recent years (1–10). In presenting our own data, emphasis will be placed upon the patients' psychological reactions to the procedure, and parameters that are related to their reactions.

Psychological Effects of Abortion—Data Prior to Legalization

Illegal abortion, performed under stigmatizing and furtive conditions, and therapeutic abortion, often accompanied by severe medical or psychiatric problems, might be expected to result in different and perhaps more serious psychological responses than would legal, socially sanctioned abortion. In reviewing the interpretive findings and conclusions of studies performed prior to legalization, one finds a variety of opinions ranging from frequent and severe sequelae (11, 12), to occasional direct or indirect problems (7, 13), to no noticeable difficulty (1, 3, 14). However, almost regardless of the source, objective data reveal low incidences of psychological complications and, in a number of cases, point to abortion as a therapeutic experience.

Undoubtedly related to the condition of illegality, few data are available concerning the psychological effects of illegal abortion. Whittemore (15), as part of a study related to illegal abortion practices in an American city with a popula-

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tion of several 100,000, interviewed over 30 women who had undergone such procedures. Criteria for patient selection were not given; the majority of patients had their abortions within six months prior to interview; however, some had the procedures as long as seven years earlier. Although ten percent had experienced postoperative infection, none of the women regretted their decision. It is of some interest that two of the patients had previously given birth to a child out of wedlock; both regretted that decision.

Gebhard et al (16), in a better controlled investigation, studied 442 American women who had had induced abortions; most of the procedures were performed illegally. Their results demonstrated only rare significant emotional sequelae. The Whittemore and Gebhard reports are perhaps of special note because of the commonly held assumptions concerning the psychological dangers of abortions.

Studies of therapeutic abortion again indicate few negative sequelae. Kummer (14) surveyed the experience of 32 psychiatrists in Los Angeles. He found that, during an average of 12 years' experience in practice, 75% of the doctors had never seen a patient with any moderate or severe psychiatric sequelae from abortion; the others had encountered such problems only rarely.

Peck and Marcus (17) studied 50 women who had therapeutic abortions prior to legalization in New York; one-half of these were done for psychiatric indications. Patients were interviewed prior to the surgical procedure and three-to-six months following the abortion. There was one case of acute negative reaction to the procedure, which was quickly relieved. Mild guilt occurred in 20 percent of cases, but was short-lived and had disappeared by the time of follow-up; 98 percent of the subjects stated that, if they were to make the decision again, they would still prefer the abortion to continuation of the pregnancy.

Even among women with serious prior psychiatric problems, the data indicate few psychological complications resulting from abortion. Patt, Rappaport, and Barglow (18) attempted to follow up 46 patients who had therapeutic abortions, with strict psychiatric indications, at Michael Reese Hospital in Chicago. Twelve patients had been lost to follow-up, and one refused to participate in the study. Among the remaining 35, who were evaluated through direct interview or physician report, the results indicated that, with rare exceptions, abortion could be considered genuinely therapeutic, primarily having a positive effect on the patients' psychological status.

Meyerowitz, Satloff, and Romano (19) evaluated the outcome of 114 therapeutic abortions performed under extremely strict indications at the University of Rochester Medical Center between 1963 and 1969. The strictness of their indications is emphasized by the fact that nine of 26 patients, who were sufficiently ill as to require psychiatric hospitalization during pregnancy, were refused permission for abortion. In spite of the severity of their emotional illnesses, most patients did well psychiatrically following abortion; 64 percent of the individuals had an immediate manifest response of relief. Approximately 10 percent had initial significant psychiatric difficulties; most of these appeared related to the underlying emotional illness. At long-range follow-up, most patients were either unchanged or better in overall psychological competence.

Finally, two studies carried out by Niswander and coworkers prior to the liberalization of the New York law indicate few negative responses to abortion, and point again to the therapeutic potential of abortion. Both studies were carried out in one of the hospitals affiliated with the State University of New York at Buffalo, where the law was interpreted liberally with nonstringent psychiatric indications. The indications for, and the milieu surrounding, the procedures were similar to those which went into effect subsequently, when the liberalized law was passed.

In the first study, Niswander and Patterson (20) followed 116 patients who underwent therapeutic abortion during the years 1963 to 1965. They found few women who regretted having the procedure. Further, among the small number of individuals who had regrets, the regrets usually were noted shortly after the abortions and tended to disappear by the time of an 8-month follow-up.

In the second study, Niswander et al (21) administered the Minnesota Multiphasic Personality Inventory test preoperatively and then again six months postoperatively to 65 patients. The results were compared to those available for a smaller group of individuals undergoing a normal pregnancy. Preoperatively, the abortion patients appeared considerably more abnormal in their psychological assessments than did the maternity patients. Both groups appeared somewhat improved at the follow-up evaluation; the abortion patients improved to a far greater extent than did the maternity patients. Especially striking findings were noted in the measures for overall adjustment and depression.

It is of interest to compare the findings of this study with the work done by Brody et al in Canada (22). The latter administered the MMPI test to 117 individuals who applied for therapeutic abortion. Of the 117, 94 were granted abortions. Those who obtained abortions were followed six weeks postoperatively; those who were denied abortions were followed six weeks postpartum. Both groups demonstrated considerable psychopathology on the basis of the MMPI test at the time of the initial interview. The individuals who obtained therapeutic abortion scored considerably better at the time of follow-up examination; no such changes were noted following delivery in the supposedly healthier group who were denied abortion. These MMPI findings are consistent with Höök's (23) interviews and evaluations in a follow-up study of 294 women whose applications for abortion were refused by the National Board of Health in Sweden in 1948 because of insufficient indications. In the original sample, 45 women were excluded from follow-up; 24 of these were excluded because their subsequent symptoms allowed them to obtain a therapeutic abortion. Of the 294 individuals who were followed, 23 percent accepted the pregnancy after the refusal and were able to handle the situation satisfactorily; 53 percent finally adjusted after having had a variety of insufficiency reactions during an 18-month observation period; the remaining 24 percent found the refusal so unfavorable that the symptoms of insufficiency, which had arisen within 18 months of the application, were still present at the time of follow-up, seven and one-half to twelve years later. A higher prevalence of subsequent incapacitating emotional insufficiency was noted among the apparently healthy women who could not qualify for abortion than among the emotionally and physically disturbed individuals who did qualify.

Psychological Impact of Legalized Abortion

Because of the newness both of state legislation legalizing abortion and the Supreme Court decisions, few studies are available concerning the effect of legal abortions. Some data have accumulated from California because of the length of existence of its liberalized legislation. Marder (24) summarized early results under the 1967 California Therapeutic Abortion Act. This modification of existing legislation represented a liberalization, but not a total legalization, of pregnancy termination. As of September 1969, approximately 609 applications had been received, and 550 had been approved. Few serious emotional problems of guilt or remorse were noted in the patients.

Levene and Rigney (25) sent follow-up questionnaires to 70 consecutive women granted therapeutic abortion for psychiatric indications in San Francisco under the liberalized California law. No serious psychiatric sequelae were found. Guilt feelings, when present at all, were short-lived.

Margolis et al (26) followed 43 patients in San Francisco for four to six months after their abortions. Although indications for abortion were liberal, five other patients were refused abortion, and only six individuals in the sample had no obvious psychiatric problems. Postoperatively, 29 of the 43 patients experienced positive psychological or growth experience or both; ten indicated no change in attitude; four had some type of negative reaction, such as guilt or fear of men. Patients' MMPI scores prior to the abortion showed abnormal elevations; at the time of follow-up, testing revealed essentially normal findings.

Ford et al (27) assessed approximately 500 clinic patients and a limited number of private patients in Los Angeles between 1968 and 1970. Their report did not include data presentation or analysis. However, they concluded that although transient mild depression was common, most individuals had a benign course after abortion.

Ford et al (28) attempted a more extensive evaluation and follow-up of 40 clinic patients who applied for abortion during the same years. Of the group, 30 were approved for the procedure with psychiatric indications; 47 percent of this group had a history of psychiatric consultation or hospitalization in the past. Five were felt to be psychotic at the initial interview. The authors were able to follow up 22 of the 30, six months postoperatively. In most of the patients, psychiatric symptoms were considerably reduced. Only three women were more disturbed, and the disturbance appeared related to the initial severe psychopathology. Similarly, as in previously cited studies by Niswander et al (21), Brody et al (22), and Margolis et al (26), patients' MMPI scores, which demonstrated considerable deviance prior to the abortion, were much improved at the follow-up evaluation.

Burnell et al (29) reported data from 924 women receiving therapeutic abortions at the Kaiser Permanente Medical Center in Santa Clara, California. All patients were given preabortion psychiatric evaluations and were offered post-abortion group therapy. More than two-thirds of the patients did not return for postabortal therapy. After review of their preoperative psychiatric reports, the authors concluded that for a majority of women the crisis of an unwanted pregnancy was a single event producing transient difficulty and that abortion provided complete relief. Among the 250 women who returned for group sessions, most expressed a sense of release from emotional tensions and symptoms. Only five percent of the smaller group experienced some postoperative symptoms; within a day or two most were able to resume their preoperative activities.

Burnell et al more recently have completed an additional study involving 300 women undergoing abortion, 300 undergoing an apparently normal pregnancy, and 300 undergoing pregnancy and placing their infants for adoption (30). They were able to obtain follow-up information on 178 of the abortion patients, 197 of the normal maternity patients, and 80 of the adoption patients six months to three years after the abortion or delivery. The follow-up adoption group was smaller because of the need for confidentiality. Although all groups experienced some psychological problems during pregnancy, those of the abortion and adoption patients were more severe than those of the normal pregnancy group. In follow-up, the abortion patients fared considerably better than those who placed their babies for adoption—25 percent of the abortion group and almost none of the adoption group reported improved adjustment; 20 percent of the adoption group and almost none of the abortion group reported worsened adjustment. Further, the initially more conservative women who underwent the pregnancy and placed their babies for adoption felt much more negative about their experience than did the abortion patients.

Data from other states parallel the positive California experience. In Colorado, on the basis of 31 return follow-up questionnaires, Whittington (31) reported a high incidence of improved symptomatology and only one patient with even possibly worse mental health.

Smith (32) in St. Louis followed 80 of 125 women who had obtained abortions after referral from the Pregnancy Counseling Service. The patients tended to be single, white, students or professional workers, and of Protestant or Catholic faith. With few exceptions, they appeared to be functioning well one to two years after abortion. Negative psychological reactions were rare both immediately postoperatively and during the follow-up period.

Freiderich and Labrum (33) in Rochester, New York, recently evaluated 300 women at the time of abortion and at 4 to 6 weeks following the procedure. They achieved 97% follow-up of the original sample and reported that patients, in general, had a positive reaction to the procedure and experienced little guilt immediately or at the follow-up evaluation.

Payne, Anderson, Kravitz and Notman (34) in a study of 102 women receiving therapeutic abortions at Beth Israel Hospital in Boston attempted to develop a broader understanding of patterns of response to unwanted pregnancy and abortion. Utilizing a prospective design and longitudinal approach, they found that reactions to an unwanted pregnancy and abortion can be understood according to the model of crisis and crisis resolution. The data showed a decrease in the intensity of painful effects between the first and last interview six months later. On the whole, they found that abortion was not a psychologically destructive procedure. They concluded that, as is true of other crises, successful mastery of the experience may have considerable maturational potential for some women.

Recently, investigators have begun to direct more attention to the differences between women seeking early abortion (usually up to 12 weeks gestation) and those undergoing saline abortion (16 to, in some cases, 24 weeks). Steinhoff (9) examined the social and demographic characteristics of abortion patients in an attempt to understand what kinds of people seek abortions and the reasons for the abortion. She concluded that abortion is most often utilized in the United States either by young, unmarried, nulliparous women or by older, married women who have completed their families. The major reason for delaying an abortion was the inability to arrange the procedure because of the patient's age or unavailability of funds.

Cushner et al (35) reported on a study of psychosocial antecedents and sequelae among patients seeking abortions at Johns Hopkins University School of Medicine. An attempt was made to compare 373 patients underoing early abortions (with curettage procedures), late abortions (with saline instillation), and women having term deliveries. They found that patients obtaining late abortions tended to be younger, more often unmarried, black, and of lower socioeconomic status than women having early abortions. Patients who obtained abortions were more frequently unmarried, of lower parity, younger, and of higher socioeconomic status than women having term deliveries. Results from the study of psychosocial antecedents revealed that the term delivery group had more visitors more frequently, told more people that they were hospitalized, more frequently held negative attitudes toward abortion, were more likely to be of lower social classes, and intended to have fewer children than the abortion groups. There were no differences in the three groups related to prior or subsequent use of contraceptives.

Kerenyi, Glascock, and Horowitz (36) interviewed 200 early abortion patients and 200 saline patients at Park East Hospital in New York at the time of the abortion. Women obtaining saline abortions were younger (and those rejected for abortion because their pregnancies had advanced beyond 24 weeks were younger still), more often unmarried, nulliparous, black, of a lower socioeconomic level, and more likely to be unemployed than women obtaining early abortions. Twice as many saline patients (29.5%) as early abortion patients did not tell the man involved about the pregnancy or refused his help. In discussing reasons for delay, the authors point to the inability of some individuals to grasp a crisis situation and act upon it realistically. Similar numbers of first and second trimester patients reported procrastination and difficulty in making the decision to have an abortion, but twice as many (71%) curettage as saline patients consulted a physician when they missed a menstrual period, and more than twice as many curettage as saline patients arrived for abortion within two months of their first suspicion of pregnancy. The "passivity" of saline patients was reflected in their generally unquestioning acceptance of the interviewer; curettage patients, in contrast, asked more questions and more often refused to be interviewed. Sixty percent of the reasons for delay, however, were seen as "correctable," relating not to patient motivation but to health care management ("red tape" or financial problems) and to basic sex education (including pregnancy and abortion information).

Experience with Implementation of a Legalized Abortion Program in New York State

As a response to the legalization of abortion in July 1970, the State University Hospital in Syracuse, New York, through the Department of Obstetrics and Gynecology, organized a program of education, contraception, and abortion services. The results of this program have been reported elsewhere (37–39), and only a brief summary will be given here. The program was designed primarily for low-income patients within the geographic area served by the hospital, although referrals from other areas were accepted as facilities allowed. Initially abortions were limited to the first 12 weeks of pregnancy, and the research evaluations, therefore, were focused upon first trimester procedures. Abortions were performed in an outpatient or inpatient operating room depending upon patient age, medical factors, and anesthesia preference. Shortly after the abortion, consenting patients received in depth interviews in order to provide them with support and to determine their reactions to the procedures. As far as possible, patients were contacted at one and again at six to twelve months after the abortion.

Between July 1970 and June 1971, information was obtained on 742 patients, ranging in age from 11 to 44 years, who had participated in one or more parts of the overall study. The patients reflected the composition of the clinic population in their marital, occupational, racial, and religious backgrounds. In all categories, the interviews revealed very few negative psychological reactions following the abortion. The predominant moods were happiness and relief; guilt, sadness, and self-anger were uncommon. Results of the four-week and six-to-twelve-month follow-ups indicated that the frequency of patient satisfaction about the original abortion decision and experience was high. The few negative feelings noted initially appeared to dissipate over time.

Because of the potential importance of conception in relationship to abortion, information was obtained concerning both the patients' past experience with contraception and their plans for contraceptive utilization in the future. Almost all of the patients planned to use contraception in the future, and the majority felt even stronger about using an effective contraceptive after undergoing an abortion.

Experience at Temple University Health Sciences Center

The program at Temple University Hospital also has been available almost exclusively for low-income patients because of the relative lack of such services, especially for mid-trimester patients, in the community. Considerable numbers of patients have been referred to the service because of difficulties in being accepted at other facilities. Because of hospital regulations, all abortions have been performed as inpatient procedures. First trimester procedures, and some second trimester procedures from 14 to 17 weeks gestation, have been done with suction curettage in the operating room, under either local or general anesthesia; most mid-trimester abortions have been performed by hypertonic saline instillation. In 1972 and 1973, intensive interviews were conducted shortly before and after the abortion procedures. These interviews focused upon two areas: a comparison of patient characteristics and emotional reactions related to first and mid-trimester abortions, and an evaluation of patients' contraceptive knowledge, fears, and use.

Three hundred women equally divided into three groups were included in the study: first trimester curettage patients, second trimester saline patients, and 14 to 17 week suction curettage patients. An attempt was made to match the three groups as much as possible; however, patients having mid-trimester suction procedures were also chosen with consideration given to patient needs and medical feasibility of the procedure. Data from distribution statistics and analyses of variance will be presented in order to demonstrate characteristics of and differences between the three groups in attitudes about and reactions to the abortion, efforts necessary to obtain the procedure, and contraceptive knowledge and availability.

Both groups of second trimester patients learned that they were pregnant later ($F = 24.1$, $p < .01$), took longer to make the decision to have an abortion ($F = 4.6$, $p < .01$), and took longer to act on their decision than did the first trimester patients ($F = 9.6$, $p < .01$). Twenty-five percent of the late curettage group and 38 percent of the saline group found out that they were pregnant after the eighth week; 14 percent of the late curettage and nine percent of the saline groups, but only five percent of the first trimester group, took more than one month to decide to have an abortion; 15 percent of the late curettage patients and 17 percent of the saline patients, but none of the first trimester patients, waited more than three weeks to try to arrange an abortion. More of the second trimester patients had difficulty finding a place to have the abortion ($F = 5.3$, $p < .01$), and had to wait longer for the abortion following the first appointment ($F = 4.6$, $p < .01$). The delay was even greater for women having a saline induction. Fewer second trimester patients as compared with first trimester patients discussed the pregnancy with the man involved ($F = 4.6$, $p < .01$).

Of patients in the first trimester group, 12 percent reported being very frightened when they realized that they were pregnant; 12 percent stated that the decision to have an abortion was a difficult one; and seven percent claimed to have initial indecision concerning whether to have an abortion or continue the pregnancy. The corresponding figures for mid-trimester patients were 25, 51, and 36 percent. Underscoring both possible ambivalence and changing relationships with the man involved (i.e. break-up of a relationship, broken promise of marriage, etc.), six to ten percent of the late curettage and saline groups stated they were happy or relieved when they found out they were pregnant; almost none of the early curettage group reported this emotion. In addition, 10 to 20 percent of the first trimester patients reported mild to moderate guilt and depression when they first considered abortion; 40 to 50 percent of the second trimester patients experienced these initial feelings about the procedure. The overall level of psychological difficulty was low among all groups following abortion. However, women undergoing saline induction reported significantly more difficulty than women undergoing either first or second trimester D & E's ($F = 4.7$, $p < .01$). Women undergoing saline inductions also reported that they were more afraid ($F = 45.4$, $p < .01$) and experienced more pain ($F = 112.5$, $p < .01$) during the procedure than those undergoing either first or second trimester D & E's. Almost all of the women, regardless of time of abortion or technique used, felt that they had made the right decision in choosing abortion; only four percent of the individuals in any group expressed uncertainty.

Differences between the three groups also were noted in contraceptive attitudes and use. Approximately 30 percent of the patients interviewed reported that they were using contraception when they became pregnant, and another 30 percent had tried unsuccessfully to obtain contraception or were misinformed about its use. Women undergoing first trimester procedures reported more consistent use of birth control pills in the past than did either of the other two groups ($F = 3.2$, $p < .05$); however, women undergoing second trimester procedures had more correct information about birth control methods ($F = 3.3$, $p < .05$). All three groups felt strongly that a woman should be able to decide the number of children that she wants. A majority of the women in all groups reported fears about the use of several forms of contraceptives, especially birth control pills and intrauterine devices. Concerns about birth control pills included fear of forgetting the pills, weight gain, nausea, headache, menstrual irregularity, infertility, hypertension, thrombophlebitis, and cancer. Concerns with intrauterine devices included fear of insertion, abdominal cramps and/or pain, heavier and/or irregular bleeding, the presence of a foreign body in one's abdomen, expulsion, perforation, infection, tubal pregnancy, and cancer. Women from all groups most frequently reported that they would use birth control pills for contraception in the future because of their effectiveness; this was especially true for women undergoing saline inductions ($F = 6.3$, $p < .01$). Among all three groups of women, the majority felt more strongly about using contraceptives in the future; the percentages were even higher for women undergoing the later procedures, especially those undergoing saline inductions ($F = 6.3$, $p < .01$).

Discussion and Conclusion

An attempt has been made to review pertinent studies from the United States concerning psychological reactions of patients to illegal, therapeutic, and legal abortions. A considerable degree of consistency has been noted in the findings.

Although illegality resulted in lessened medical safety, furtiveness, and a relative paucity of scientific investigation, the limited data which were available suggested few negative psychological sequelae. Women who were able to obtain the procedures usually were determined, healthy, and socially mobile individuals.

Logically, one should have expected the highest incidence of psychological problems in individuals obtaining a therapeutic abortion prior to legalization. The stringency of the laws and the indications for the procedures resulted in only the most psychiatrically disturbed individuals qualifying for abortions.

Indeed, some of the studies demonstrated a small incidence of postoperative psychiatric disturbance in individuals with prior severe psychopathology; the postoperative difficulty almost uniformly appeared related to the existing psychiatric disturbance rather than to the procedure. Further, the overall existence of postoperative psychological problems in individuals qualifying for therapeutic abortion was remarkably low. In most cases, psychiatric and psychological evaluations demonstrably improved both in attitudes and behaviors. Patients who were denied an abortion because of insufficient psychiatric problems fared considerably worse postdelivery than did the apparently more emotionally disturbed individuals who qualified for and received an abortion.

Results from the relatively recent experience with legalized abortion have been confounded by the fact that some of the statutes have provided liberalized, but not truly legalized, conditions. Medical or psychiatric indications, albeit of a lesser magnitude, frequently have been necessary to obtain a legal abortion. Some patients have been denied procedures because of apparent lack of indication. To the extent that data have become available, they have been consistent with the findings already cited. For most women, abortion has had few, if any, significant psychological sequelae. In the limited number of cases where feelings of guilt or depression have been present, they have tended to be mild and transient in nature. On the whole, the experience has led to further emotional maturation and resolution of conflict. In the rare instances where psychiatric disturbances have been noted postabortion, they have appeared related to existing psychopathology rather than to the procedure.

Our data are consistent with these overall findings. Individuals, regardless of religion or race, have availed themselves of the services. Abortion has not been viewed as an alternate form of contraception; rather, convictions about the need for future contraception have been strengthened by the procedure. Postabortal feelings of guilt and depression have been relatively infrequent. Relief and happiness have been the predominant moods.

Our more recent data indicate that individuals undergoing second trimester abortion have had more delays in obtaining medical care, more difficulties in decision making, more difficulties with the procedure, and slightly more postabortal feelings of guilt and depression than individuals undergoing a first trimester procedure. Some of these appear related to differences in the overall life situation that contributed to the delays in obtaining medical care and to the difficulties in decision-making. Further, some of the difficulties with the procedure may reflect a realistic situation, since, in general patients undergoing saline induction experience more discomfort during the procedure. However, it should be emphasized that negative feelings have been rare among all groups and that among individuals with follow-up evaluations satisfaction has been high.

The discrepancies in contraceptive knowledge between patients having first and second trimester abortions may be related to the differences in number of medical visits that second trimester patients make before receiving definitive care and to differences in the extent of their counseling. Differences in attitudes and future contraceptive plans may relate to patient characteristics and differences between the procedures. The fears reported about various contraceptives, especially birth control pills and intrauterine devices, are of interest. This area would appear worthy of further study to determine the degree to which similar fears are present in women of reproductive age and whether there are differences between women obtaining abortion and women who are successful contraceptors. Once again, our recent data confirm that women obtaining abortions feel strongly, and if anything more strongly, about using effective contraception in the future and that they do not view abortion as an alternate form of contraception.

Obviously, additional in-depth investigations are required. More baseline data are needed concerning such issues as factors that may influence patient motivation, differential impact of procedures at different stages of gestation, potential effects of abortion on interpersonal relationships and family patterns, and possible long-range positive or negative effects of abortion. More service-oriented material is needed, including objective assessments of the relative value or lack of value of routine counseling, comparison of the effects of various types of counseling and/or counselors, determination of the relationships between service components and patient outcome, techniques for prediction of future successful contraceptive use, and development of methods for identifying patients with problems who might benefit from specific forms of therapy.

In conclusion, it should be emphasized in this time of increasing availability of services that for most women abortion appears to be accompanied by few, if any, significant negative psychological sequelae. More often, abortion appears to lead to individual growth and resolution of problems. The option to choose abortion, and to obtain it, seems in most cases to promote mental health.

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The Impact of Voluntary Abortion on American Obstetrics and Gynecology

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Prologue

The right to abortion is the foundation of Society's long struggle to guarantee that every child comes into this world wanted, loved, and cared for. The right to abortion, along with all birth control measures must establish the Century of the Wanted Child. . . ." Lawrence Lader (1).

Our American founding fathers enshrined in our Declaration of Independence the magnificent dream of the pilgrim immigrants in the words, "The right to life, liberty, and the pursuit of happiness." However the concept that a right to healthy life coexists with other rights and that it imposes obligations on governments and other social organizations has developed much more recently. Those who wrote about the rights which seemed crucial around 1776 could hardly foresee the succeeding 200 years of scientific and technical achievements in the treatment and prevention of disease, nor could they even dream of the magnitude of the economic impact of those advances. With a continent to be populated and with the maternal and infant mortality rates of the day, the problem of a "population explosion" was inconceivable. Thus, over the next century the major concerns in relation to any intervention in a pregnancy that was not desired were toward avoiding maternal death. The legal, moral, and social climate created as a result of legislative actions in the nineteenth century flowed over into the twentieth century and conditioned the education, the philosophy, and the patterns of practice of most of the physicians actively practicing in North America in the 1950's and 1960's (1–4).

From the 1930's to the 1950's, as urbanization proceeded rapidly, the magnitude of the induced abortion problem began to weigh heavily in the statistics of departments of obstetrics and gynecology, and of urban departments of health such as that of New York City (5–7) and the physicians who were closest to the problem began to write extensively of its toll of suffering and death (7, 8).

Of course, Margaret Sanger had begun her efforts at organizing birth control services and disseminating information in 1912. But it required 53 years of sorrowful American history in this area before the United States Supreme Court affirmed a basic right of privacy, and by that decision rendered unconstitutional a myriad of state laws and other rules and regulations which interfered with the dissemination of information and services related to birth control.

As far back as 1936, the historian Norman E. Himes was able to survey the progress in the dissemination of contraceptive knowledge and practices, and

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devoted two chapters of an exhaustive work to the concept of "democratization of birth control." Himes clearly documented that "the desire to control conception is a well nigh universal phenomenon." He concluded his historical treatise with these cogent words: "These moves are in the right direction; even if they have been unduly delayed. We may yet catch up with Soranos, Aetios, and the Arabians and Persians. Who knows? Whether the curve of history will be projected into the future now depends on the physicians and on the kind of support they get from the general public and especially from legislators" (9).

Since the majority of American laws which addressed the question of pregnancy interruption permitted it only when the pregnancy was deemed to threaten the life of the mother, the middle decades of the twentieth century saw the origin of the concept of committees for therapeutic abortion (2, 10). This pattern of collective decision-making developed to provide support for the practitioner who performed the procedure; namely, the support of a recorded decision of a committee of consultants who confirmed by majority or unanimous action that a threat to the life of the mother did, in fact, exist. The structure and rules of function of these committees became a part of hospital medical staff bylaws and departmental rules and regulations, as well as subjects for review by various accrediting agencies.

Hall (11) emphasized the great variation in the manner in which these committee activities functioned in different institutions, and indeed in the same institution according to the economic status of the patient, or according to the physician from whom the patient happened to be seeking her care, etc. In surveying 60 hospitals throughout the country, Hall found an abortion to delivery ratio from one in 20 to one in 4,161 in private services, and from one in 138 deliveries to one in 4,339 deliveries in ward services in the same hospitals. The mean ratio for all private patients, however, in these hospitals was one abortion to 300 deliveries, and the mean for all ward patients was one abortion to 945 deliveries. There were, of course, hospitals that reported no abortions for either ward or private patients. In another group of university services which did not involve private patient care the abortion to delivery ratio was one abortion to 1,417 deliveries.

Hall concluded: "The obstetricians of America must individually and collectively review these vital issues in an effort to establish a more uniformly humane birth control ethic."

A vast amount of medical, general public and political effort before and after the establishment in 1965 of the right to contraceptive information and services culminated in the emotion-packed switching of the vote of one New York State Assemblyman from "NO" to "YES" on April 9, 1973. This vote led to New York State enacting abortion legislation which fundamentally made abortion until the 24th week of gestation a matter to be resolved between the patient and her physician alone. With no requirement that the patient must be a resident of New York State to obtain this medical service, citizens from many other states as well as New York State's own residents used this new freedom in very large numbers (12).

While some other states in the nation had preceded New York State by several years in the matter of adopting some liberalized form of abortion legislation, no other state had made such a clear and sweeping decision in favor of treating abortion like any other medical decision, as a matter to be decided strictly between the patient and her physician. On January 22, 1973, the Supreme Court of the United States rendered decisions in the abortion question which were essentially consistent with the New York State indicating only that in the second trimester of pregnancy states might properly establish regulations concerning abortion as long as such regulations were designed only to safeguard the health of the mother.

The Philosophical Impact

The wide range of differences in abortion practice in different institutions and within the same institution for different practitioners or different economic levels of patients was not maintained without considerable stress and strain on the organized and personal relationships among physicians, not to mention the stresses on the processes of rationalization and justification by individual physicians (2). It is highly probable that those institutions and physicians who adhered most rigidly to criteria for pregnancy interruption consistent with the laws which specified a threat to the mother's life as the sole indication for pregnancy interruption were the most comfortable with the status quo. Many institutions performed pregnancy interruptions infrequently, usually for far advanced medical disease or for some very narrow set of psychiatric indications usually requiring a bona fide act of attempted or threatened suicide as proof of the gravity of the psychiatric illness. While many individual physicians or entire staffs did not agree with the legal strictures, they practiced what the law required and taught that pattern of practice to cadres of new specialists in the field (2).

However, where members of medical staffs individually or in large numbers began to question that rigidity, they began to seek and find support primarily from their psychiatric colleagues on therapeutic abortion committees, who were willing to certify that the pregnancy was a threat to the life of the pregnant woman in circumstances where the threat of or attempt at suicide was not so overt. Psychiatrists and obstetricians became partners in their efforts to meet the need of larger numbers of women to terminate unwanted pregnancy—and to endeavor to do it within the medical care system. In the soul-searching that went on in that era, the question not infrequently was asked: "If I decline to assist this woman in abortion procurement through normal medical channels, and thereby she seeks abortion from an irregular practitioner, and since I understand the risks of her procuring an abortion in that way, is it not true that the pregnancy comprises a risk to her life?" In some such manner, as indicated in Hall's survey, some hospitals and staff met the abortion needs of larger numbers of women while others met the needs of very few or none at all (10, 11).

The contrast to the situation which prevails in New York State since 1970 and increasingly everywhere since the U.S. Supreme Court decision in 1973, can hardly be overstated. Increasingly, abortion can be dealt with in a manner that is very nearly identical to that of other urgent medical care situations. Now, the physician no longer needs to rely on hypocritical subterfuge. He needs only to search his own conscience as to whether or not he properly and sympathetically can render a high quality of service to the patient who requests a pregnancy termination—and then in each individual case be reasonably certain that he is acting in the best interests of that particular patient and in response to her voluntary request. As with other medical care situations, if he can never perform the procedure, or if in this circumstance it is his judgment that the procedure should not be performed, he can in accordance with good medical practice refer the patient to other sources of consultation and advice for the problem which she presents.

I have described all of the above at length because the impact of this new situation with respect to pregnancy interruption (and with sterilization and contraception) is not just like a breath of fresh air—but indeed is a veritable and steady trade wind sweeping away decades of confusing and degrading dialectics in this whole area of medical practice.

It has been both interesting and disappointing to observe some of the difficulties experienced by physicians trained under the previous rules as they strive to adjust to this new atmosphere. Some of the imagined and real problems related to the early concentration of abortion demand in a relatively few locations throughout the country. Physicians in those settings experienced unusual workloads, and thus developed concerns about the deterioration of other programs of patient care, and deterioration of the quality of training in obstetrics and gynecology. The redistribution of abortion care throughout the entire country following the US Supreme Court decision will certainly alleviate this problem of abnormal workload. The same logistics problem affected all staffs, and particularly on conscientious nursing personnel, who found the burden of high volume of abortion care monotonous and repetitious. Such staffs often developed negative feelings about abortion based upon the excessive workload, and not because they objected to the general principle that a woman who wished to have an abortion should have the opportunity to do so. Of course, ambivalence between stated and intellectual approval of the new philosophy versus deep-seated emotional feelings developed through years of adherence to a different philosophy was not always easy to alter. This ambivalence has tended to make many persons from the disciplines of nursing, medical social work, and obstetrics and gynecology feel that the woman requesting termination of pregnancy automatically requires very sophisticated counseling. That all of us experience many life situations in which the sympathetic understanding, and perhaps professional counseling, of others would be helpful is undisputed and that in our present culture many such experiences are "toughed through" without such help may only mean that an opportunity for personal growth and strengthening was missed. Nor can one deny that the occurrence of a pregnancy in circumstances in which it is not desired is a disturbing experience– and that a decision to terminate the pregnancy certainly poses an opportunity for a great deal of personal help and guidance.

However, some of the rationale advanced by advocates of extensive pre- and postabortion counseling is faulty. The evidence has grown with the passage of time and with the very large volume of abortion services rendered that there are few (indeed almost no) serious emotional or psychiatric sequelae which can be traced directly to the decision to terminate an unwanted pregnancy, or to the implementation of that decision. On the other hand, there is strong evidence that the continuation of pregnancy which has not been wanted through refusal to concur in a request for pregnancy termination can and does produce undesirable results (13).

The Medical Impact

A most important and dramatic immediate impact of nearly universal availability of medically safe abortion services has been a substantial decline in the level of indices traditionally used to indicate the quality of maternal and newborn care. Pakter and many others have begun to document in convincing fashion declines in the maternal death rate related to abortion and, surprisingly, declines of comparable magnitude in maternal mortality from nonabortion causes (12, 14). Similar reports are emerging with respect to declines in perinatal mortality (15). It has long been recognized that both maternal and newborn risks in out-of-wedlock pregnancies are increased. For the first time since records have been maintained, New York City data indicate decreasing rates of out-of-wedlock births, thus giving promise of even further and sustained declines in the levels of maternal and infant mortality and morbidity rates (12). It is clear that the obstetrician/gynecologist will no longer need to devote very much effort to saving the life of the woman who has procured a clandestine abortion either by some grossly traumatic manipulation, or who has remained secluded after the initiation of sepsis until pelvic infection had reached such an advanced stage that not even the most modern and heroic measures could salvage all; both types of patients are rapidly disappearing from the scene (16–19).

Abortion under medical auspices is not an innocuous procedure. Indeed, it is the conviction of many within the medical profession that the political campaigns waged to change abortion legislation misled, through exaggeration of simplicity, many women to underestimate very real medical problems which persist despite the many technical advances in the performance of abortion.

Actual maternal mortality resulting from interruption of pregnancy by suction or D and C during the first trimester is extremely small—0 in 170,519 abortions in New York City in the second year of its program (12) or 1 in 56,273 abortions in the Joint Project for the Study of Abortion by Tietze (20).

The major complication rate in the JPSA survey was 0.6% for patients having suction abortion procedure only, who resided locally, and who had a follow-up report available. The major complication rate for patients having saline abortion was 2.4% (20). It is encouraging to note that the overall mortality rates have declined with the passage of time as the entire medical care system became more familiar with the problems surrounding abortion and the modern technology associated with it– e.g., from 4.6 deaths per 100,000 abortions in New York

City the first year to 3.5 in the second year (12). Tietze also observed sharp declines in all suction complication rates over 12 months of JPSA reporting (20).

Of course, the greatest contribution to safety takes place as women learn to seek early pregnancy diagnosis and make early decisions concerning their wishes for termination or for pregnancy continuation.

The most recent thinking and practice in this area is the procedure called "menstrual induction" or "menstrual extraction." The former term is favored by those who are convinced of the advantage of inducing menstruation either routinely or whenever it is delayed past its expected onset, even without the confirmation of presently available pregnancy testing. Others in the profession continue to feel that the decision to invade the uterine cavity with an instrument should be based upon better evidence than menstrual delay. It is probable that most in the field reject the concept of routine menstrual induction simply for menstrual and social convenience.

The legal approval of voluntary interruption of pregnancy has undoubtedly advanced the medical and surgical technology of pregnancy interruption. Much of the rapid progress in the evaluation of the possible role of prostaglandins in pregnancy termination would have been impossible, at least in America, without the changed legal climate of the past several years. The current generation of obstetrician/gynecologist trainees has received training and experience in pregnancy interruption which far exceed in most instances the experience of their teachers. The new obstetrician/gynecologist has a first hand experience based upon large numbers of pregnancy interruptions—an experience which has provided superb technical skills in amniocentesis, vacuum evacuation of the uterus, assessment of complications occurring with such procedures, and a flexible awareness of the varied approaches which work effectively when complications of these procedures occur.

There are no definitive reports of prospective studies which specify the long term complication rates of voluntary abortion by present techniques. We need to know whether or not the performance of one or more voluntary abortions affects the subsequent rates of a number of undesirable complications of reproduction—and if it does, the extent of the changed risks of: a) involuntary infertility; b) ectopic pregnancy; c) incompetent cervical os and mid-trimester abortion; and d) unsatisfactory outcome of pregnancies carried beyond the mid-trimester; that is, low birth weight infants, or other pregnancy, labor or delivery complications. These rates will be meaningless unless they are compared with control groups of women who are known with great certainty not to have had voluntary abortion. The studies will need to go forward from approximately the present time with patients who are receiving the benefit of current abortion practices—not even those which were in effect two or three years ago. It would seem reasonable to assume, for example, that the less forceful dilatation of the cervix that is required, the less might be the subsequent risk of cervical incompetence or complications of the later period of desired pregnancy. The use of laminaria for more gentle cervical dilatation is only in its infancy in this country. Similarly, if cervical dilatation is not required at all (as in the menstrual induction technique with a 4 or 5 mm soft plastic cannula) the risks of introducing even minimal infection may be less than in procedures that require any substantial cervical dilatation—and thus secondary infertility rates may be expected to be lower as less traumatic procedures become more widely available and applied to earlier gestations. The same may be true if parenteral or vaginal prostaglandins become acceptable abortifacients.

The question is frequently asked: "Will abortion availability reduce the utilization of contraceptive measures?" On the basis of available evidence, there is thus far no reason to believe that women who have equal access to a full range of contraceptive services will elect repeated abortion in place of such preventive measures. In Harlem Hospital, family planning clinic visits increased 25% in the first 12 months following introduction of abortion services (14). Women will continue to strongly prefer pregnancy preventive measures to pregnancy termination unless some major evidence arises to change our present knowledge concerning the risks involved in the use of the two most effective contraceptive methods—the intrauterine devices and the oral contraceptive agents. One other factor which might change present use patterns significantly would be a campaign of gross misrepresentation with respect to the comparative risks. Thus far, even the most sensational claims regarding risks involved in the use of these two effective and highly acceptable preventive measures have consistently failed to influence their use except in a transient manner.

Only time will answer the question of whether women generally will begin to develop a reliance upon abortion instead of upon contraceptive measures. Another beginning indication that such is not the case emerges from a review of residents of New York City who have had their second or later abortion since voluntary abortion became available July 1, 1970. During the 12-month period July 1, 1971 through July 30, 1972, repeat abortions comprised 3.94% of 63,783 abortions reported from New York City residents. A sampling of the total repeater group indicated that only 47.3% were not using a contraceptive method. And of those not using methods, an analysis of the dominant reason given for non-use suggests that approximately 70% would have been using a method if they had received appropriate counseling assistance and/or services (21).

The total impact of abortion discussion and practice will lend even greater support to efforts to more safely and effectively prevent the occurrence of unwanted pregnancy. The anti-abortion debate and the real problems associated with abortion should give impetus to the increased allocation of research support into the mechanisms of human reproduction and to the search for more effective and safer contraceptive methods than are now available. It should also provide leverage to orient the distribution of contraceptive supplies (especially nonprescription items) toward consumer needs.

The Social and Economic Impact

The legal situation which rendered some states and the cities within them focal points for abortion services caused the entrance into the health care delivery system of persons and organizations which would not otherwise have been so involved. Persons who had not previously had access to health dollars found ways to derive "referral fees," transportation fees, abortion clinic management incomes, and profitable excess incomes from employing part-time physicians as technicians in their abortion facilities. But as abortion services become more widespread, these opportunities for making excessive profits through the delivery of abortion care are diminishing.

The pluralistic nature of abortion services which developed has served to modify the price structure in the patient's favor. But the location in which the majority of future abortion services will be rendered cannot be clearly foreseen. It seems probable that in the relatively near future the earliest procedures, (termination of pregnancies up to about 45 days' amenorrhea), will become very commonly performed office procedures, whether or not the medical establishment agrees that that is the best location for the procedure. The fact that the economic overhead is lowest in the private office is an important factor; but also the simplicity and privacy of a visit to a physician's office contrast so strongly with the complexity of procuring a brief operative procedure in many of our hospitals, especially in the larger ones.

The factors of the delivery of abortion services in locations other than conventional hospitals, the involvement in abortion care of many citizens who had not previously been associated with health care in any way, the emphasis of various women's movements towards emancipation of women from all-male dominance (including the dominance of male physicians), and a widespread interest throughout the health establishment in expanding the roles of non-physicians in health care delivery converged to create pressures from some quarters to train non-physicians in the actual performance of abortion procedures. While it is possible to train people with widely different backgrounds to perform specific technical tasks as part of a broadly competent medical and health team, the prospect of persons with limited technical skills assuming independent responsibility for surgical and/or other health care of the patient without continuing supervision and continued learning is a development that will serve badly the cause of pregnancy termination and a range of other health services. The performance of pregnancy termination by current methodology involves complications, which, although of low frequency, may be dramatic and may require all of the health team in an acute care institution with specialist skills in anesthesia, shock, pelvic surgery, urology, etc., to preserve life and reproductive function.

If one were to accept the New York City situation as a base for projecting approximate number of abortions to be requested in the next several years (22), it is difficult to imagine why the United States should require nonphysicians to undertake this surgical procedure. Considering that New York City has had in many areas rather strong family planning programs, but also that it has large numbers of citizens who are disadvantaged socioeconomically, it seems reasonable to accept the 1971 abortion-to-live birth ratios as intermediate compared to other more or less advantaged areas of the USA. The abortion-to-live birth ratios in New York City in 1971 were 372.9 for white residents and 562.8 for non-white resident (12). If one applies these ratios to a hospital service that accomodates a delivery volume of, let us say, 3,000 births annually, the problem becomes one of handling roughly 1,000 to 1,500 operative procedures annually—

or four to six 15 20 minute procedures per working weekday—a very small work-load indeed. And that volume of hospital abortion work may be reduced as office procedures become more widely practiced and as contraception knowledge and use increase.

In the wider social arena, the impact of ceasing in the main to bear and rear children who have not been truly wanted surpasses the foresight of even those trained in the study of social pathology. It has never been possible to calculate the social cost of unwanted childbearing, especially in urban America where such a large proportion of it has been associated with single parent child rearing. But it is certain that the beneficial social impact of childbearing by choice will have a parallel impact upon obstetrics and gynecology, and in time will reduce the frequency with which many pathologic conditions are seen.

Epilogue

The semantic controversy over the use of the words abortion, contraception, birth control, family planning, and planned parenthood will probably not abate quickly. Pragmatically, of course, "birth control" is what the individual woman or couple has as their ultimate goal; and, whether verbalized in those words or not, that is clearly what the individual means when the words "family planning" or "planned parenthood" are personalized to her or his own life situation. But it seems certain that the moral, legal, and political debates, particularly as they focus on the use of public funds for providing pregnancy prevention services versus pregnancy termination services, will continue to waste human energy in emotional and semantic discussions. But the impact of widely available voluntary abortion as the ultimate mechanism of "family planning" when conception prevention measures have failed, for whatever reason, will eventually reduce the importance of the semantic aspects of this debate.

The information gathered by Bumpass and Westoff (23) indicated that in the years 1960–1965, before voluntary abortion had become significant within our medical care system, births to married women occurring in that five-year period were unwanted by both spouses at a rate of 17%, and unwanted by at least one spouse at a rate of 22%. We shall never know the extent to which women at that time utilized nonmedical sources for abortion procurement. However, it seems certain that more socially acceptable abortion services within the medical care system (combined of course with constantly broadening availability of contraceptive services and information) will cause a marked decline in the high proportions of births described as "unwanted." And this will apply to persons of all ethnic and religious groups as it appears that women seek birth prevention on the basis of personal perception of their individual need for it—and do not conform to prohibitions publicly enunciated by secular or clerical leaders (24).

The impact which abortion may make in the short term on the absolute number of births in the U.S. probably is quite considerable. Tietze has calculated that in New York City, adjusting for changes in age distribution of the female population, the annual number of live births between 1970 and 1972 declined by 25% (37,800) and his estimations attribute about one-half of that decline to legal abortion (25).

Considering the apparent advantages (combined social and obstetric) to childbearing in the 20–29 year age group, it seems certain that obstetric complications of pregnancy will decline in frequency, (26, 27). A growing demand for a perfect and planned reproductive experience places new needs for exacting quality control upon the discipline of obstetrics and gynecology, but also generates in our patients a very high level of receptivity and cooperation with recommended regimes of care. These salutary attitudes of patients bearing planned and wanted pregnancies are in marked contrast to the fatalistic disinterest of many higher parity women who previously crowded our public prenatal clinics for their almost annual relatively unwanted births.

The frequency of long-term psychiatric complications of voluntary abortion, extremely small even at present, will be further reduced as the overall social climate becomes more accepting of abortion as a part of normal health care throughout the nation. Differences in the way that abortion is regarded by the administrators of fiscal reimbursement mechanisms (insurance, Medicaid, etc.) tend to perpetuate a certain level of collective guilt or feeling of inappropriateness with respect to this type of health care—and the removal of these differences of treatment would be another step toward ensuring that the patient seeking abortion care was treated in exactly the same manner as a patient seeking any other kind of health service.

The practice of contraception may undergo a gradual change with the broad availability of voluntary pregnancy interruption. In the climate of the late 1950's and early 1960's, when abortion was relatively unavailable, a near-zero pregnancy failure rate was an important, indeed indispensable, criterion for an acceptable contraceptive method. The known pregnancy rates with the intrauterine device were recognized by family planning clinic administrators to be substantial deterrents to a wider acceptance of the intrauterine device. It seems probable that when voluntary abortion is generally available, hormonal or intrauterine device methods of contraception (or methods not yet in use) which have negligible rates of demonstrated discomfort or complication to the user may become more acceptable, even if pregnancy failure rates with such regimes are slightly higher than the failure rates experienced with current widely used pills and devices.

The impact of Lader's "Century of the Wanted Child" promises to greatly enhance the opportunities of the obstetrician-gynecologist to become the leader of the primary and comprehensive health care team for women. For decades in the forefront of preventive or "health" care but now increasingly freed from many of the acute surgical and technical problems of the past century (7, 28), the obstetrician-gynecologist will strengthen skills already being practiced and will cultivate new skills to aid women to develop and maintain normal health and function.

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Infant Mortality in Sweden—Implications for the United States*

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Sweden has had the lowest reported infant mortality rate among all countries of the world for a number of years, and it continues annually to achieve this record. Because of this consistent record of achievement, it is important that obstetricians, pediatricians, and other community health workers observe services and patient care in Sweden in an effort to determine the possible associated factors. This article will summarize some of the factors in Sweden which may be related to their low infant mortality rate, and will attempt to answer certain questions:

1. What is the status of infant mortality in Sweden?
2. What is the organization of maternal health services and child health services in Sweden which may be playing a role in infant mortality?
3. What are the implications of these factors and circumstances for the United States?

The Status of Infant and Perinatal Mortality in Sweden

Infant Mortality in the Various Countries of the World

In 1971, according to data reported to the United Nations, Sweden had an infant mortality rate of 11.1 per 1,000 live births, the lowest reported rate of any country in the world. In 1971, the reported rate in the United States was 19.1 (Table I), ranking sixteenth that year.

Infant Mortality in Sweden and the United States

Infant mortality in Sweden has experienced a virtually uninterrupted decline from 1751 to the present time (Fig. 1) (1).

From 1950, the infant mortality rate in Sweden has remained consistently below that of the United States. The Swedish infant mortality rate has been in continuous decline from 1950 to 1973, except for the years 1967 1968, when there was a slight increase. From 1950 to 1973, the infant mortality rate declined 52.9 percent in Sweden, compared with a decline of only 39.7 percent in the United States. In 1950, the infant mortality rate in Sweden was 21.0—28.1 percent lower than that of the United States; in 1973, the rate in Sweden was 9.9—43.8 percent lower than that of the United States (Table II).

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TABLE I

Reported Infant Mortality Rates per 1,000 Live Births for Selected Countries: Various Years 1969–1971

(United Nations Statistical Yearbook: 1972. New York 1973, Table 21, pp. 89–94.)

Country	Year	Rate
Sweden	1971	11.1
Netherlands	1971	11.1
Finland	1971	11.8
Japan	1971	12.4
Norway	1970	12.7
Denmark	1970	14.2
France	1971	14.4
Switzerland	1971	14.4
New Zealand	1971	16.5
Lichtenstein	1969	16.7
Australia	1971	17.3
United Kingdom	1971	17.9
England & Wales		17.5
Scotland		19.9
N. Ireland		22.7
Germany (East)	1971	18.0
Hong Kong	1971	18.4
Canada	1970	18.8
United States	1971	19.2
Ireland	1970	19.6
Singapore	1971	19.7
Belgium	1971	19.8
Israel	1971	20.4
Czechoslovakia	1971	21.6
Luxembourg	1971	22.5
USSR	1971	22.6
Germany (West)	1971	23.2
Bulgaria	1971	24.9
Austria	1971	26.1
Greece	1971	27.0
Spain	1970	27.9
Italy	1971	28.3
Poland	1971	29.5

No state in the United States in 1973 had an infant mortality rate as low as that of Sweden. Utah had the lowest reported infant mortality rate of 13.0 in 1973, compared with 9.9 in Sweden in the same year.

Infant Mortality by Age in Sweden and the United States

Of the total infant mortality rate of 9.9 per 1,000 live births in 1973 in Sweden, 7.8 (78.8 percent) was neonatal and 2.1 (21.2 percent), postneonatal. In the United States in 1973, of the total infant mortality rate of 17.6, 12.9 (73.3 percent) was neonatal and 4.7 (26.7 percent), postneonatal.

From 1960 to 1973, the infant mortality rate in Sweden declined 40.4 percent, compared with a decline of 32.3 percent in the United States. The neonatal mortality rate in Sweden declined 43.5 percent from 1960 to 1973, compared with a decline of 31.0 percent in the United States. By contrast, the United States had a greater decline in the postneonatal mortality rate from 1960 to 1973 than Sweden (35.6 percent compared with 25.0 percent) (Table III).

The decline in infant mortality in Sweden covers all parts of the first year of life. Perinatal mortality has also shown a decline from 1940 to 1970 (Fig. 2) (2).

In the year 1969, a lower proportion of infant deaths in Sweden, compared with the United States, occurred in the age periods "under 1 day," and 28–364 days. As a result Sweden had a higher proportion of infant deaths in the age periods 1–6 days, and 7–27 days (Table IV).

Analysis of data for the white infants only in the United States shows that their

TABLE II

Live Birth Rates per 1,000 Population and Infant Mortality Rate per 1,000 Live Births. United States and Sweden: 1950–1955, 1960–1973

(United States: National Center for Health Statistics: Vital Statistics for the United States. Annual Reports; and Sweden: National Department of Health and Welfare. Central Bureau of Statistics. Population Changes. Stockholm 1973.)

Year	Live Birth Rate		Infant Mortality Rate	
	United States	Sweden	United States	Sweden
1973	14.9	*	17.6	9.9
1972	15.6	13.8**	18.5	10.8
1971	17.2	14.1	19.1	11.1
1970	18.4	13.7	20.0	11.0
1969	17.8	13.5	20.9	11.7
1968	17.5	14.3	21.8	13.1
1967	17.8	15.4	22.4	12.9
1966	18.4	15.8	23.7	12.6
1965	19.4	15.9	24.7	13.3
1964	21.0	16.0	24.8	14.2
1963	21.7	14.8	25.2	15.4
1962	22.4	14.2	25.3	15.4
1961	23.3	13.9	25.3	15.8
1960	23.7	13.7	26.0	16.6
1955	25.0	14.1	26.4	17.4
1950	24.1	14.2	29.2	21.0

* Not available.

** Provisional.

infant mortality rates have been consistently higher than those of Sweden. In 1973, the infant mortality rate in Sweden was 9.9, while for whites in the United States it was 15.2. In 1973, the neonatal mortality rate in Sweden was 7.8, while for whites in the United States it was 11.5. In 1973, the postneonatal mortality rate in Sweden was 2.1, while for whites in the United States it was 3.7 (Tables III and V).

The percentage decline in infant, neonatal, and postneonatal mortality rates among whites in the United States has been consistently less than that in Sweden in the period 1960–1973 (Tables III and V).

The Fetal Death Ratio in Sweden and the United States

The fetal death ratio (fetal deaths of at least 28 weeks gestation per 1,000 live births) in Sweden was higher than that of the United States until 1963. In the late 1960's the ratio in Sweden was only four-fifths that of the United States.

The Perinatal Death Ratio in Sweden and the United States

In the period 1966–1972, the perinatal death ratio in Sweden has been about 30 percent lower than that of the United States (Table VI).

TABLE III

Infant, Neonatal, and Postneonatal Mortality Rates, United States and Sweden: 1950, 1955, 1960–1973

(United States: National Center for Health Statistics. Published and unpublished data; and Sweden: Central Bureau of Statistics. Population Changes. Stockholm.)

Year	Mortality Rate per 1,000 Live Births					
	United States			Sweden		
	Infant	Neonatal	Postneonatal	Infant	Neonatal	Postneonatal
1973	17.6	12.9	4.7	9.9	7.8	2.1
1972	18.5	13.7	4.8	10.8	8.7	2.1
1971	19.1	14.2	4.9	11.1	8.8	2.3
1970	20.0	15.1	4.9	11.0	9.2	1.8
1969	20.9	15.6	5.3	11.7	9.3	2.4
1968	21.8	16.1	5.7	13.1	10.9	2.2
1967	22.4	16.5	5.9	12.9	10.5	2.4
1966	23.7	17.2	6.5	12.6	10.3	2.3
1965	24.7	17.7	7.0	13.3	10.6	2.7
1964	24.8	17.9	6.9	14.2	11.7	2.5
1963	25.2	18.2	7.0	15.4	12.3	3.1
1962	25.3	18.3	7.0	15.4	12.4	3.0
1961	25.3	18.4	6.9	15.8	13.1	2.7
1960	26.0	18.7	7.3	16.6	13.8	2.8
1955	26.4	19.1	7.3	17.4	*	*
1950	29.2	20.5	8.7	21.0	*	*
Decline 1960–1973	32.3%	31.0%	36.9 %	40.4%	43.5%	25.0%

* Not available.

TABLE IV

Infant Mortality Rates by Age: United States and Sweden. Selected Years, 1969–1973

(United States: National Center for Health Statistics. Published and unpublished data; and Sweden: Central Bureau of Statistics. Population Changes. Stockholm.)

	Rate per 1,000 Live Births							
	United States 1969		Sweden 1969		United States 1972		Sweden 1973	
	Rate	Percent	Rate	Percent	Rate	Percent	Rate	Percent
Total.......	20.9	100.0	11.7	100.0	18.5	100.0	9.9	100.0
Under 1 day	9.2	44.0	3.7	31.6	7.9	42.7	3.4	34.3
1-6 days.........	4.9	23.4	4.5	38.4	4.3	23.2	3.5	35.4
7–27 days...........	1.5	7.2	1.1	9.4	1.5	8.1	0.9	9.1
Total, under 28 days	15.6	74.6	9.3	79.5	13.7	74.1	7.8	78.8
Total, 28–364 days..	5.3	25.4	2.5	20.5	4.8	25.9	2.1	21.2

TABLE V

Infant, Neonatal, and Postneonatal Mortality Rates in the United States by Color: 1940, 1950, 1960–1973

(National Center for Health Statistics. Published and unpublished data.)

Year	Mortality Rate per 1,000 Live Births					
	White			All other		
	Infant	Neonatal	Postneonatal	Infant	Neonatal	Postneonatal
1973	15.2	11.5	3.7	28.8	19.8	9.0
1972	16.3	12.3	4.0	29.0	20.6	8.5
1971	17.1	13.0	4.0	28.5	19.6	8.9
1970	17.8	13.8	4.0	30.9	21.4	9.5
1969	18.4	14.2	4.2	32.9	22.5	10.4
1968	19.2	14.7	4.5	34.5	23.0	11.6
1967	19.7	15.0	4.7	35.9	23.8	12.1
1966	20.6	15.6	5.0	38.8	24.8	13.9
1965	21.5	16.1	5.4	40.3	25.4	14.9
1964	21.6	16.2	5.4	41.1	26.5	14.6
1963	22.2	16.7	5.5	41.5	26.1	15.4
1962	22.3	16.9	5.5	41.4	26.1	15.3
1961	22.4	16.9	5.5	40.7	26.2	14.5
1960	22.9	17.2	5.7	43.2	26.9	16.4
1950	26.8	19.4	7.4	44.5	27.5	16.9
1940	50.3	*	*	89.2	*	*
Decline 1960–1973	33.6%	33.1%	35.1%	33.3%	26.4%	45.1%

* Not available.

TABLE VI

Perinatal Death Ratios (Fetal Deaths of at Least 28 Weeks Gestation plus Deaths under 1 Week of Age, per 1,000 Live Births). United States and Sweden: 1966-1972

(United States: National Center for Health Statistics. Published and unpublished data; and Sweden: Central Bureau of Statistics. Population Changes. Stockholm.)

Year	United States	Sweden
1972	21.4	14.0
1971	21.9	15.7
1970	23.2	16.5
1969	24.2	16.3
1968	27.1	18.4
1967	27.1	18.9
1966	27.7	19.0

Wedlock Status

From Table VII it is evident that the proportion of out-of-wedlock births in Sweden has been consistently increasing since 1963, and is considerably higher at this time. It has been about twice that of the United States and about 3–4 times that of United States whites. However, the Swedish rate has been only about one-half of United States "others." It is of interest that, in spite of this

TABLE VII

Births out of Wedlock (ratios) per 1,000 Live Births. United States by Race, and Sweden: Various Years, 1930–1972

(United States: National Center for Health Statistics. Published and unpublished data; and Sweden: RFSU Statistik. Befolkningen, Sexualvanor, Aborter, Gonnoré, Sexualbrott, Internationellt. Stockholm, May 1973, 99 pp.)

Year	United States				Sweden
	Total	White	All others		
			Total	Negro	
1972	124	60	403	439	251
1971	113	56	373	405	216
1970	107	57	349	376	194
1969	100	55	325	349	*
1968	97	53	312	*	*
1967	90	49	294	*	151
1966	84	44	276	*	146
1965	62	40	263	*	138
1964	68	34	245	*	131
1963	63	31	236	*	126
1962	59	28	230	*	*
1961	56	25	223	*	*
1960	53	23	216	*	94
1959	52	22	218	*	*
1958	50	21	212	*	100
1957	47	20	207	*	101
1956	46	19	204	*	102
1955	45	19	202	*	99
1954	44	18	199	*	98
1953	41	17	191	*	97
1952	39	16	183	*	99
1951	39	16	183	*	101
1950	40	17	180	*	98
1949	37	17	168	*	94
1948	37	18	165	*	*
1947	36	19	168	*	*
1946	38	21	170	*	*
1945	43	24	179	*	96
1940	38	20	168	*	118
1936	*	*	*	*	135
1930	*	*	*	*	173

* Not available.

increase in the proportion of out-of-wedlock births, the infant mortality rate in Sweden has declined.

Birth Weight

The incidence of low birthweight in the United States is almost twice that in Sweden (Table VIII) (2). In the United States, the incidence of low birthweight in whites is one-half that in all other infants (3).

It is well known that birthweight and gestational age are significant factors in survival of the infant (Table IX). The lower the birthweight, the higher the mortality.

Maternal Health Services in Sweden

Maternal health care is delivered through maternal health centers, of which there are 282 in Sweden—99 of Type I and 183 of Type II (4). In 1970, 115,402

TABLE VIII

Percent of Live Births 2500 Grams and Under. United States and Sweden: 1950–1972

(United States: H. C. Chase: Trends in Low Birth Weight Ratios, United States and Each State, 1950–1968. U.S. Govt. Printing Office, June 1973. Washington, D.C., 48 pp; and National Center for Health Statistics. Published and unpublished data; and Sweden: G. Geijerstam: Low Birth Weight and Perinatal Mortality. Public Health Reports, 84:939–948, 1969.)

Year	United States	Sweden
1972	7.7	*
1971	7.7	*
1970	7.9	4.4
1969	8.1	*
1968	8.2	*
1967	8.2	*
1966	8.3	*
1965	8.3	4.6
1964	8.2	4.6
1963	8.2	*
1962	8.0	*
1961	7.8	*
1960	7.7	*
1959	7.7	4.5
1958	7.7	*
1957	7.5	*
1956	7.5	*
1955	7.6	*
1954	7.6	*
1953	7.6	*
1952	7.6	*
1951	7.5	*
1950	7.5	*

* Not available.

TABLE IX

Percentage Distribution of Live Births by Birth Weight, United States, 1965, and Sweden, 1965 and 1970; and Early Neonatal Mortality (within 7 days) by Birth Weight, Sweden: 1965 and 1970

(United States: National Center for Health. Trends in Prematurity, United States, 1950–1967. Vital and Health Statistics, Series 3, No. 15, Jan. 1972. DHEW Publication No. (HSM) 72–1030; and Sweden: G. Geijerstam: Low Birth Weight in Perinatal Mortality, Public Health Reports, 84:939–948, 1969; and National Board of Health and Welfare Public Health in Sweden. Stockholm 1972, 143 pp.)

Birth Weight Group (in grams)	Birth Weight (percent) United States 1965	Birth Weight (percent) Sweden		Early Neonatal Mortality Within 7 Days (percent) Sweden	
		1965	1970	1965	1970
1000 or less . .	0.6	0.2	0.2	88.1	85.6
1001–1500 . .	0.7	0.4	0.4	47.6	41.2
1501–2000 . .	1.5	1.0	0.9	15.4	12.8
2001–2500 .	5.5	2.9	2.9	4.8	3.4
Total					
(2500 grams or less)	8.3	4.5	4.4		12.2
(2501 grams or more) . . .	91.7	95.5	95.6		
Total	100.0	100.0	100.0		

women received care there, with an average of 11.9 visits per woman. Maternal health centers Type I are connected with a hospital department of obstetrics and gynecology, and headed by an obstetrician. Maternal health centers Type II are headed by a district medical officer or some other physician. They are sometimes combined with a child welfare center. At present, approximately 95 percent of pregnant women receive prenatal care through these maternal health centers. On an average, each pregnant woman makes about four visits to the doctor and eight to the nurse-midwife.

Standards for maternity care have been developed (4). This includes medical and dental care, and such laboratory tests as screening for Rh and ABO incompatibility, syphilis, and bacteriologic culture for suspected gonorrhea. Optional tests include cytologic screening for cervical cancer, examination for detection of asymptomatic bacteriuria, and chest x-ray during the second trimester. Contraceptive advice is a regular part of postnatal care.

Courses for expectant parents are given by nurse-midwives. Most prenatal care is provided by nurse-midwives. Whenever a complication is suspected, the woman is referred immediately to an obstetrician; if confirmed, she will continue under the care of the obstetrician. Thus, there is screening for high risk women, and their care is then the responsibility of the obstetrician. In rural areas, this is a problem because of the unavailability of obstetricians.

Over 99 percent of all deliveries take place in hospitals (5). Most normal deliveries are done by nurse-midwives. Women with complications are delivered by obstetricians. The system of medical and hospital care makes this easy to implement, except in remote rural areas.

Maternal health care is free under the National Health Service, as are medications, including iron and vitamins.

Presently, there are more than 50 hospitals with departments of obstetrics and gynecology, with full-time medical staff, encompassing about 70 percent of the total 3,600 maternity beds.

Maternal Mortality

Sweden has one of the lowest maternal mortality rates in the world. Annually there are 9–10 maternal deaths in Sweden per 100,000 live and still births (Table X). Major remaining causes are infection, toxemia, and hemorrhage. Abortion has virtually disappeared as a cause of maternal death.

Abortion in Sweden

A woman considering abortion may go to one of the special advisory centers on abortion. These centers sometimes are independent institutions, but as a psychiatric evaluation of the applicant may play a role in the procedure, some of them are associated with psychiatric departments. The applicant is given a thorough gynecologic examination to check on the state and duration of pregnancy, and on the advisability of an abortion. Authorization for abortion can be obtained either from the National Board of Health and Welfare or from two doctors in consultation. The special Social-Psychiatric Committee (which is composed of an obstetrician, a psychiatrist, a geneticist, and a lay woman) reviews reports on the applicant, which usually are submitted by a psychiatrist, obstetrician, and social worker. When permission for an abortion is granted, the procedure must be done in a public hospital by an obstetrician or surgeon. As a rule, it must be done before the end of the 20th week of gestation. For teenagers, it is relatively easy to secure an abortion. For example, in the years 1965–1969, 85 percent of those under 15 years of age had their applications for abortion approved.

TABLE X

Maternal Mortality in Sweden: Various Years, 1955–1970

(National Board of Health and Welfare. Public Health In Sweden. Stockholm 1972, 143 pp.)

	1955	1960	1965	1966	1967	1968	1969	1970
Infection	5	3		1		2	3	2
Toxemia	17	10	6	3	4	2	3	2
Hemorrhage	6	7		4	4	2	1	1
Uncomplicated abortion	9	4	2	2	1		2	
Abortion with fever			1		1			
Other complications	16	14	8	4	7	4	2	6
Total maternal deaths	53	38	17	14	17	10	11	11
Total maternal deaths per 100,000 live and still births	49	37	14	11	14	9	10	10

The cost of abortion is covered by National Health Insurance. Some counties have an abortion bureau which makes no charge for abortion. In other counties, the patient may have to pay 12 kroner.

As to reasons for the need for a change in the abortion law, these may be summarized as follows: (1) the law is interpreted more liberally than it is written; (2) in some regions, doctors have a more rigid, judgmental attitude; (3) the procedure given in the law may be too time-consuming.

In 1970, of 16,100 abortions (6), 7,645 were done on unmarried women, 6,796 on married women, and 1,659 on divorced women. Of the 16,100, 163 were done on women under 14 years, and 3,425 were done on women 15 19 years of age.*

Sex Education in Sweden

Sweden is one of the few countries where sex education is compulsory in the schools. It was introduced into the school curriculum in the 1940's and became a required course in 1956. The first government syllabus (Handbook) was published in 1945, and was revised in 1956. It was again revised in 1968. The government recently set up a Swedish State Committee for Sex Education, which has just completed its report (7). The Committee has accepted sex experience in the teenager.

The handbook on sex education covered the following topics: structure and function of the sexual organs; development of fetus and pregnancy; labor; sex and youth; children born out of wedlock; abortion; venereal disease; contraceptives; sterilization; menopause; sexual abnormalities; welfare measures to help in setting up a family; welfare measures in pregnancy, confinement, and nursing; and welfare measures for the care and training of adolescents. Sex education has been taught in biology, social studies, religion, and other classes. In addition to general sex education in the classroom, the school nurse does considerable sex education with teenagers on an individual basis.

Family Planning in Sweden

The status of family planning in Sweden varies among the 25 counties and 3 large cities. In general, considerable information about family planning is available—via sex education in schools, information on hospital intrapartum and postpartum services, and at the time of the postpartum visit to the Maternal Health Center.

In regard to family planning service, there is considerable geographic variation; two examples will illustrate the situation. In the city of Stockholm, advice is free; the patient pays the full price for oral contraceptives and the IUD In Umeå (in the north of Sweden, a community of 60,000 with a medical school), the patient pays 12 kroner for the visit to the doctor, plus the full cost of supplies; in Umeå, there is a 9-month waiting list for family planning services.

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* Editors' note: Abortion at the request of the pregnant woman, without specified indications, through the 18th week of gestation, was legalized in Sweden as of January 1, 1975. Almost 26,000 legal abortions were performed in 1973.

Infant Health

National planning insures the provision of an intensive care unit for the newborn in each region of the country, located at a medical school. Some transport service is available. A pediatrician is required to be present at all deliveries of high risk infants in university and teaching hospitals. An effort has been made to train physicians and nurses in techniques of resuscitation of the newborn.

Neonatal screening is done routinely in the hospital for phenylketonuria, galactosemia, tyrosinuria, and fructosuria. A register on congenital malformations is kept by the National Board of Health and Welfare; reporting is done by maternity and newborn services with a pediatrician; data are sent monthly from the hospital to the National Board of Health and Welfare.

There are approximately 1,300 child welfare centers in Sweden; 405 are of Type I (connected with a Department of Pediatrics of a hospital and directed by a pediatrician); 894 are of Type II (located in other facilities and directed by a medical officer). About half the children are supervised by Type I and the other half by Type II centers. The other main staff of the child welfare centers consists of nurses; some effort is being made now to add psychologists and social workers to strengthen the mental health aspects.

The service is completely free of charge. It consists of preventive measures, including medical examinations, screening for vision and hearing, immunization, and counseling (8). All mothers receive a home visit by a nurse within two weeks of delivery. A baby is brought to the child welfare center at the age of 2–6 weeks. Almost 100 percent of children in the first two years of life, and 73 percent of the 2–7 year olds, are supervised by the child welfare centers. On an average, each infant makes 5 visits to the doctor and 3 to the nurse, who, on the average, also makes about 3 home visits to infants. Immunization is done for smallpox, diphtheria, tetanus, pertussis, and poliomyelitis. BCG vaccine is given before the baby is discharged from the newborn service. Counseling includes feeding, hygiene, child-rearing, safety, and accident prevention. Efforts are made to encourage breast feeding; in 1970, 35 percent of babies were breast fed for two months or more, 15 percent for 4 months or more, and 7 percent for 6 months or more.

Special regulations have been drawn up by the National Board of Health and Welfare, and adopted for use by the child welfare centers (4).

Implications for the United States

Possible general factors contributing to the low infant mortality rate in Sweden include the fact that Sweden is a smaller country, with a smaller, more homogeneous population. It is a country with a high per capita income, second only to the United States. The people as a whole have a high standard of living, based upon a more even distribution of the wealth of the country. There is a high level of education, and the standard of housing and general nutrition is high. Sweden has both national health insurance and a national health service, making it possible for the people to receive medical and hospital care and drugs at nominal additional cost. There is more even distribution of the amount and quality of medical and health care. The social security system of benefits for sickness, pregnancy, and children means a basic family support system for vulnerable parts of the population.

There are also more specific factors contributing to the low infant mortality rate in Sweden. For example, in the field of maternal health, a high percentage of deliveries takes place in hospitals. There is a country-wide network of maternal health centers, which are attended by practically all women during pregnancy. The maternal health centers (except those in rural or isolated areas) are connected with a department of obstetrics of a hospital, and are staffed by an obstetrician from the hospital. This means that a health delivery system exists to screen pregnant women, identify those of high risk, and bring them under the care of an obstetrician. It is possible to transfer women with complications to hospitals with better maternity services, if necessary. Regionalization of perinatal services for high risk mothers and infants has been developed. The long-standing availability of abortion services and more recent development of contraceptive services have reduced the number of unwanted births.

In the field of child health, the development of regional perinatal centers, including intensive care units for the newborn and some transport service, is a factor contributing to the lower infant mortality rate in Sweden. The much lower incidence of low birth weight in Sweden is a major factor in its low infant mortality rate; possible explanations for this are better nutrition, more extensive coverage of the country for prenatal care, and the removal of the stigma on pregnancy out of wedlock. A pediatrician is present at all deliveries of high risk women in most obstetric services. There has been training of personnel in resuscitation of the newborn. There is a countrywide system of child welfare centers with a very high rate of registration and supervision of infants. Except in rural and isolated areas, the child welfare centers are connected with a department of pediatrics of a hospital and are staffed by a pediatrician.

If the United States is to move ahead more rapidly in reduction of infant mortality, certain general measures should be considered. These include efforts to improve the general level of living, housing, nutrition, employment, and educational status of all of the population. The creation of a system to provide maternity benefits and children's allowances needs consideration. Our country also must confront the issues of national health insurance and a national health service, which have the possibility at least of providing a more equal distribution of medical and health care for all of our people.

A national plan is needed to guarantee and provide the services so that all pregnant women have easy access to safe prenatal, intrapartum, postpartum, and contraceptive care. There must be a mechanism built into a better developed system to make it possible to screen all pregnant women early in pregnancy, to provide health education for all of them, to identify early in pregnancy those at high risk for medical and social reasons, and to provide them with more specialized and extensive services. The best maternity care our country can provide has to be available to all high risk pregnant women. One possible method is that basic maternity care may be provided by well trained nurse-midwives or by obstetric nurse-practitioners, with the highly trained obstetrician concentrating his efforts on high risk women. Outlying and satellite services should be tied to district or regional obstetric services of high quality for the care of high risk women. The concept of regional perinatal care for high risk mothers and infants, which is moving quite rapidly now in the United States, must be fully implemented. Intensive effort should be made to improve the nutritional status of pregnant women, adolescents, and preadolescents in an effort to reduce the incidence of low birth weight. Abortion and family planning services need to be made freely available to all who wish to use them.

Obstetric and pediatric inpatient, outpatient, and outlying services (including maternal health, infant health, child health, and family planning services in the community) must be brought together so that there can be continuity in mothers and children cared for and considered together as a unit.

The problem of low birth weight and other high risk infants requires a unified approach, both from the viewpoint of prevention and management. An intensive care unit for the newborn should be available in each community or region, with rapid transport service. Each delivery of a high risk woman requires personnel trained in the emergency care of high risk infants.

Similarly, a network of preventive services is necessary, providing the basic services of health appraisal, health education, immunization, guidance in infant feeding, nutrition, and accident prevention. Earlier identification of high risk infants and their families, for medical or social reasons, is essential. Problems of child abuse and sudden infant death are assuming greater importance in postneonatal mortality, and require earlier identification of families who need help. It is possible that the pattern for the future may be for the basic preventive services to be provided by pediatric nurse practitioners, with early identification of those infants and families in need of special medical and social care and assistance.

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Letter to Alan Guttmacher concerning the United Nations World Population Conference, Bucharest, Romania August 19–30, 1974

LOUIS M. HELLMAN, M.D.* AND HONORABLE CASPAR W. WEINBERGER†

Dear Alan,

Had you been alive and well you would have been present at Bucharest and undoubtedly published your own characteristically pungent comments. Had you been unable to make the journey, many of your friends would have given you their varied impressions of what happened and what was accomplished.

So far the delegation has made very few public comments on the conference, the press generally has been derogatory, and the various bodies and members of the Tribune, which was only distantly associated with the governmental delegation, have presented a variety of views.

I was fortunate enough to be part of the official delegation and to travel with Secretary Weinberger. While I had no previous experience with international conferences and make no pretense to know all that went on in so large and complex an international meeting, I was present at the preconference meetings. I was familiar with the preconference position of the United States, and saw many of the reasons for changes in our attitude as the conference progressed. I would have told you of my impressions of the conference had it been possible. This letter is a poor substitute for the conversational give-and-take we might have had, but it will have to serve. The letter is strengthened by Secretary Weinberger's willingness to contribute some of his own impressions and to act as coauthor.

Kurt Waldheim, Secretary General of the United Nations, attempted to set the theme of the conference by stating at the opening that he hoped the conclave would "make an important contribution to the solution of the problem of the discrepancy between the growing population all over the world and the shortage of food." Among the opening speeches, one by Roy Jackson of FAO sounded an even more somber note on the world's food supply. Unfortunately, the urgency of these messages was lost because of the politicization of the conference. The injection of politics and the polarization of the delegations were neither unexpected nor, in the long run, necessarily deleterious.

The previous world population conferences of 1954 and 1965 were attended by experts, mostly demographers, who generally were in ideologic harmony, although they may have disagreed on particular issues. They were, however, neither responsible to the body politic nor did they represent political decision-makers. Thus this present conference was, I believe, unique because for the first time in history it brought government leaders, meeting in a common forum, face to face with population issues. From this viewpoint, the results of the conference, especially the hesitancy, the wordiness and inconsistencies in the World Plan of Action are more understandable.

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One hundred and thirty-seven nations were represented by over 1200 registered delegates. In addition, there were present the Tribune (composed of non-governmental agencies), the Youth Conference, and representatives of UN organizations and of four liberation movements, and many other groups, making this the largest international complex of gatherings ever held. The US delegation comprised thirty-one individuals.

In addition to the Plenary, there were four committees: Development, Environment, Family, and Plan of Action. These committees were constantly attended by our representatives and/or their alternates. Our delegation was well balanced, well assigned, and adequately staffed, so that we were able to attend all the meetings. Although we had scant time for organization, I cannot speak too highly of the skill and devotion of our members who presented professional and well-organized positions.

We delivered to the Bucharest Conference President Ford's first message to an international meeting:

> You are meeting on a subject that in the true meaning of the word is vital to the future of mankind: How the world will cope with its burgeoning population.
>
> The rapid growth of the human race presents one of the greatest challenges of man's ingenuity that we have ever encountered. We already know a great deal about the causes of growth, but we know very little about the best ways to deal with its consequences. That must remain one of our primary mutual concerns for the remainder of this century.
>
> The policies and programs you recommend to solve these problems could affect the peoples of all our nations as well as generations yet unborn. I send you my wishes for the greatest success in your deliberations and pledge that the United States will work unceasingly with you in seeking solutions that are both sound and right.
>
> *Gerald R. Ford*

Our purpose was to reexamine our differences with other countries, to reconcile them wherever possible, and seek out better avenues of approach to our world population problems than those we have explored with minimal success in the past. We had every intention of maintaining a low profile so that we could not be accused of promulgating a reduction of population growth in the poorer developing nations to the advantage of the developed. Because of the positions of some of our delegates before the conference began, we became identified with set targets of population growth both for the developed and the developing world.

While targets may be useful if set by an individual nation for its own use, they often are unrealistic and stand as a red flag if set by well-to-do nations as goals for poorer nations. Further, it may not be the number of people that is significant, but rather the rate at which these numbers accumulate. No one could have expressed the purpose of the conference more eloquently than did Sr. Carillo Flores, Secretary-General of the conference, when he told the delegates: "We are here because we love life, not because we fear it."

The major problem we face today is how man best can fit the limited resources of a finite world to the limitless potential of his reproductive instincts—or vice versa. To say that we were not all agreed on the answer to that equation—or even that it was stated in the proper order—would be a grave understatement. Certainly, the nations of the world did not go to Bucharest anticipating a chorus of agreement on problems so complex that they reach into the very core of man's religious, cultural, emotional, and economic experiences.

No rational observer of the world scene today could deny the existence of serious social and economic problems affecting, most acutely, the developing nations. An attempt to correct these injustices without also considering the population problem would be both ineffective and absurd.

At Bucharest, the old gambit of causal reasoning from correlation was utilized—"developed nations do not have a population problem; therefore, pay for our development and everything will be fine." The upside-down logic of that approach has been demonstrated time and time again in countries where hard-won advances in economic growth have been partially or totally absorbed by unchecked population growth. Our delegation won recognition of the fact that population programs are an essential part of social and economic development. Our emphasis was directed at those countries which now have to import a large part of the food supply for their existing population, and have the highest rates of population growth. Nevertheless, no one expected that the nations represented at Bucharest, rich and poor alike, could or would agree instantly and unanimously to reduce their birth rates. Indeed, there were some who insisted that their economies needed more, not fewer, human hands.

As we said previously, the Bucharest World Population Conference was unique. Unlike many conferences that can barely put plan on paper, we adopted by acclamation a World Population Plan of Action—imperfect and lacking a sense of urgency—nevertheless, a heartening sign of recognition that the overwhelming problems of mankind in an interdependent world demand and will benefit from a global attack on population growth.

Worldwide agreement was reached at Bucharest on at least four basic propositions:

1. The basic human right of couples and individuals to decide the number and spacing of children, and to have the information, education, and means to do so, and to exercise that right responsibly, taking into account the needs of living children, of children yet unborn, and of the community. [This proposition carries important extensions of the Teheran Declaration of 1968. It recognizes individuals as well as couples, and, more importantly, it concerns itself with responsible parenthood both from the community and personal viewpoints.]
2. The corresponding obligation of governments to provide the information, education, and means to all their peoples to decide the number and spacing

of children, along with recognition that national programs and policies should be consistent with internationally and nationally recognized human rights.

3. The concept of quantitative goals to be set by 1985 to reduce infant mortality, increase life expectancy, and reduce fertility rates—recognizing that each nation has the sovereign right to set its own goals, or none at all.
4. The proposition that specific measures should be taken to facilitate the participation of women in all spheres of public life. [Most of those who spoke to this question emphasized better educational opportunities as the key to elevating the role of women in national life, and looked for lower fertility rates as an incidental result.]

Because of the close relation between population and food, you might have been interested in the United States position on the issues of food and natural resources. The sudden, enormous requirements of many nations in 1972 and 1973 for food imports have alarmed the world. The most urgent needs were met, but world food reserves are the lowest in decades, and prices of basic foods have risen sharply. All US farmland formerly held out of production has been returned to production. There is little margin of safety anywhere. Part of this increased demand is due to the growing affluence of many countries, but a larger part is due to population increase.

The annual world population increase of some 80 million people, nearly all in countries which already must import part of their food supply, plus slight improvements in diets for some, will increase world food requirements about $2\frac{1}{2}$ percent per year on the average, but in many developing countries the annual increase in demand may be closer to 4 percent. The UN Second Development Decade of the Seventies calls for a 4 percent annual increase in agricultural production. Unfortunately, in the first three years of this decade the increase has averaged only 1 percent.

Agricultural specialists tell us that if all goes well with weather, soil, water, fuel, fertilizer, and if incentives are provided to farmers, the world can produce the food requirements for the United Nation's median projection for the populations of 1985 and 2000, albeit with borderline diets for many and starvation for some. Unfortunately, even if these events occur, much of this food will not be where the people are. The countries with the greatest needs simply will not be able to produce enough food to meet their needs. In many of them, most of the good land with adequate water is already in use; fuel and fertilizer are scarce, expensive, and usually require foreign exchange. In some large regions, population growth weakens an already fragile environment in ways which threaten long-term food production. Thus, overgrazing, deforestation, land exhaustion, soil erosion, and water pollution of many kinds increase in areas that can least afford these problems. In addition, the impact of natural or other disasters is greater because more people are trying to exist under marginal and quite vulnerable conditions.

Most developing countries will be dependent on continually increasing imports. If their population grows as projected, their import requirements for basic cereals alone will rise from 24 million tons in 1970 to some 95–112 million tons in the year 2000. The costs of these imports would rise from about $2.5 billion in 1970 to $15–$18 billion (in 1974 prices) in the year 2000.

We all know that most predictions of doomsday do not materialize, but surely there is cause not only for grave concern but, even more important, for specific action to reduce the rate of population growth and to increase the world's food supply.

There is a growing demand on the world's natural resources, especially by the industrialized countries. In the United States, 87 percent of the natural resources we use come from within our country. A considerable part of these, as well as imported resources, are sent to other countries as finished products. Population growth, increasing affluence, and expanding industrialization in all countries increase the demand for resources.

Although the Conference at Bucharest was aimed at population, of necessity it recognized the inextricable relations of food, economy, and resources. Other conferences will have to deal with the details of these issues. Paragraphs 68, 69, and 70 of the World Population Plan of Action, however, are concerned with social and economic policies which will be vital for eventual resolution.

Under the aggressive leadership of the government of Mexico, the conference consistently reinforced sovereignty of nations to decide population policies. While the US supported this position, the exercise of national sovereignty may have to be limited at some time in the future if the population question is as crucial as some believe. Obviously, the world is not ready for this type of "one-world" thinking at this time.

It might be of advantage, in considering the implications of the world conferences yet to come, to examine the political dynamics of Bucharest in slightly greater detail. The clash between the lesser developed countries and the developed countries set the political/ideologic tone of the conference. The LDC's, with the exception of Asian and some Latin American countries, considered attempts to reduce population growth before fundamental restructuring of society and significant economic development to be totally futile. They were supported in this position by the communist bloc. For other reasons, Argentina and the Holy See opposed any emphasis on the limitation of population and sought to delete any mention of family planning and contraceptives.

The Asian countries, with the exception of the People's Republic of China, and occasionally India, fully supported the objectives of the United States government and seemed well aware of their population problems. The African countries led by Algeria generally supported the new International Economic Order and favored the theme: "Economic development is the best contraceptive."

The actions of the Latin American countries were mixed. Some, for example Colombia and Venezuela, are beginning to move in a positive fashion on family planning. Others are staunchly pronatalistic. Brazil, previously pro-population growth, surprisingly indicated that it was prepared to make family planning services available to the poor; the rich already have such services.

Early in the conference the United States abandoned its low profile position in response to repeated derogatory use of characterizations such as colonialistic, imperialistic, neocolonialistic, hegemonistic, etc., by the communist countries and the countries of the Third World. Not only did we successfully answer these onslaughts but we took prime leadership in pushing for global action. We received strong support from the United Kingdom and Canada, and occasional support from the French government. The Holy See was the only delegation which announced it was not part of the conference consensus on the World Plan of Action. Ironically, there was a parallel between the stance of the Holy See and that of the People's Republic of China in spite of their vast ideologic differences. They made every effort to delete references to family planning and fertility-related goals or population policy.

The United States delegation received numerous, unsolicited favorable comments at the end of the conference, even from critics. Our leadership role, particularly in the World Plan of Action Working Group, was particularly appreciated. Our description of our own Family Planning Program was unique among conference attendees. We were not afraid to vote (almost 50 votes were taken in the working group, but none in the Plenary), and we took our occasional defeats as well as our victories with equanimity, setting an example for the workings of the democratic process.

Although our nation does not have a written population policy with administrative or legislative goals, the three branches of our government and our informed electorate have by voluntary action created policies which influence population in ways perhaps more significant than any stated policy.

President Nixon's administration produced a landmark study relative to "Population Growth and the American Future." The Congress enacted a family planning services program which is administered by the Executive Branch. Organized family planning programs now reach nearly 3½ million low-income women, and private physicians reach another 1.2 million who otherwise would not have access to them. Some form of government-subsidized family planning service is now available in 85 per cent of the counties in the United States and efforts are being made to reach into the others.

A National Center for Population Research supports a large biomedical and behavioral sciences program of research in human fertility and its control. The US Agency for International Development also sponsors general research programs overseas.

For more than a decade, the lower courts and the Supreme Court have enacted decisions which affirm the right of individuals and couples to control their own fertility. Our people are informed of these actions by a free press; and by voluntary means they have reduced their fertility to the replacement level. This trend has been nationwide—occurring among rich and poor, among the majorities as well as the minorities. Should the trends continue, fertility will probably equalize among the various social and economic groups and population stability will be reached in about 60 years.

We were nearly the only country at Bucharest that held up its own program for examination. The example caused expressions of surprise and applause.

Bucharest did not end on August 30, 1974. The Population Conference bears an intimate relation to the Food Conference which was recently held in Rome, to the Conference on Women held in Mexico City in 1975, and that on Urban Development scheduled to be held in Vancouver, B.C. in 1976.

Furthermore, certain articles of the World Population Plan of Action provide for continued monitoring, review, and reappraisal of new and emerging population trends and policies.

It will be our policy to support the World Population Plan of Action; to cooperate fully in international efforts to deal with the intertwined problems of population, food, and development; to help other countries that want our assistance; and to do our part in providing financial help, especially to the poorer countries. We hope other financially able countries, particularly the newly rich nations, will do the same. There is a tremendous opportunity to practice some of the obligations they and others have been quite willing to assign to the United States in the past. We intend also to seek greater opportunities for progress in the developing countries through international trade, investment, and technologic assistance.

In dealing with the strains which recently have been imposed on the world economic system, we would like to see international agreement on special measures for those poorer countries which have been damaged severely by the higher cost of imported energy, food, and fertilizer but have not benefited significantly by higher prices for the goods they export.

Those of us who participated in the Bucharest Conference returned home more deeply aware of the nature of the population crisis in many countries, and more aware of the deeply held beliefs of our friends in those countries. In addition, all of us, whatever our disagreements on specific aspects of the problem, are agreed on the urgent need for action, but we are acutely aware that simplistic and quick resolutions are the stuff that dreams are made of. Solutions when they come, and they will, will require dedicated, complex, and cooperative political action.

Louis Hellman
Caspar Weinberger

Editors Note

The United Nations World Population Conference held in Bucharest, Romania in August, 1974 was the first international, governmental conference on population problems in history. The participation of the United States in that conference was far removed from the position taken only two decades earlier by President Dwight David Eisenhower that government had no business in the area of family planning. Alan Guttmacher was preeminent among those who contributed to this change in the attitude of the US government and to the development of a world climate which led to this conference.

It is a particularly fitting epilogue to this memorial issue for Alan Guttmacher to include a report on that Bucharest conference; and even more appropriate that the report be from Dr. Louis M. Hellman, a lifelong friend, colleague, and coworker of Alan's, and currently serving as Deputy Assistant Secretary for Population Affairs, Department of Health, Education, and Welfare, and the Honorable Caspar W. Weinberger, Secretary of Health, Education, and Welfare.

The work to which Alan Guttmacher was committed goes on.

Joseph J. Rovinsky
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Editorial

It is the custom, wherever possible, to salute a newly arriving chairman with an announcement in the Journal. On this page we introduce Dr. Steven M. Podos, Professor and Chairman of Ophthalmology, Mount Sinai School of Medicine of The City University of New York and Director of the Department and Ophthalmologist-in-Chief of The Mount Sinai Hospital.

David A. Dreiling, M.D.

STEVEN M. PODOS, M.D.

Doctor Steven M. Podos was appointed Professor and Chairman of the Department of Ophthalmology at the Mount Sinai Medical Center July 1, 1975. Doctor Podos graduated Summa cum Laude from Princeton University and was a member of Phi Beta Kappa and Sigma Xi honor societies. In 1962 he graduated from Harvard Medical School and then served a medical internship at the University of Affiliated Hospitals in Salt Lake City, Utah. This was followed by a residency in ophthalmology at Barnes Hospital and the Washington University School of Medicine in Saint Louis, Missouri.

Doctor Podos was also a Clinical Associate in the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland from 1967 to 1969. He returned to the Department of Ophthalmology at Washington University in 1969 and became Professor of Ophthalmology in 1974.

Doctor Steven Podos is best known for his work on glaucoma, an area in which he has conducted basic research and written extensively for the past decade. He is a Fellow of the American College of Surgeons and is on the Editorial Boards of Investigative Ophthalmology, American Journal of Ophthalmology and Survey of Ophthalmology. Doctor Podos, along with Dr. Edward Cotlier, was awarded first prize at the XXI International Congress of Ophthalmology held in Mexico City in 1970 for their exhibit on Dislocated Lenses Associated with Congenital and Hereditary Systemic Disorders.

In his new position, Doctor Steven Podos will be combining his research, clinical, and administrative skills along with innovative educational programs that will benefit members of the Department of Ophthalmology as well as the staff of The Mount Sinai Medical Center. We extend our warmest wishes to Doctor Steven Podos for a long, productive, and happy career at Mount Sinai.

Keith M. Zinn, M.D.
Contributing Editor

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Egas Moniz, Pioneer of Angiography and Leucotomy*

ANTÓNIO R. DAMÁSIO, M.D.

Egas Moniz was one of the few clinical neurologists to be awarded the Nobel Prize in Physiology and Medicine. He received this honor in 1949 for his development of prefrontal leucotomy; but the world fortunately associates him, more often than not, with the pioneering of cerebral angiography, his other remarkable contribution to the neurosciences. This is the year of his centenary and the occasion seems appropriate to honor the man and the work.

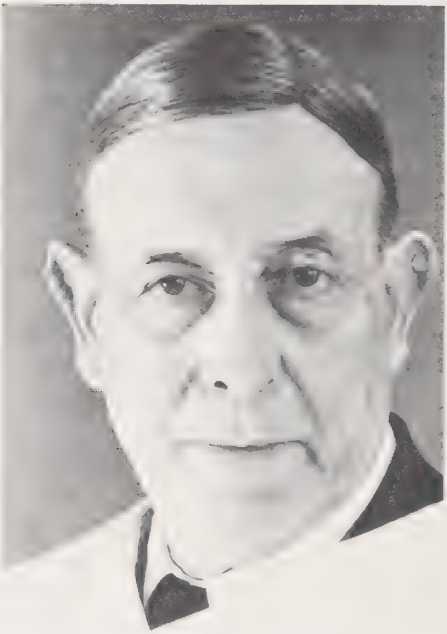

FIG. 1. Professor Egas Moniz.

Egas Moniz was born November 1874 in a small town in the north of Portugal. He finished his medical studies in 1899 at the ancient University of Coimbra where he soon became a Doctor in Medicine and a Professor of Medicine, with a special interest in the diseases of the nervous system. In those early days the renown of Moniz related to his activity as a democrat fighting against monarchy. This resulted in two convictions and two interludes

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From The Centro de Estudos Egas Moniz, Lisbon Faculty of Medicine, Lisbon, Portugal.

* Presented at a special seminar for the Department of Neurology on November 1, 1974.

Requests for reprints should be sent to: Dr. António R. Damásio, Department of Neurology, University Hospital, Iowa City, Ia. 52242.

in jail before a republic was established in 1910. But he was also famous for a scandalous book on sexology written in 1901, a bestseller in its own time, in which he brought the risqué work of Kraft-Ebbing and Freud to the conservative, religious shores of Portugal.

It was only in 1911 that he came to Lisbon and was appointed to the newly created chair of neurology. Part of his neurologic training had been made in France during the glorious turn of the century period. Pitres, in Bordeaux, was his first professor. Later he went to Paris in the heyday of Babinski, Pierre Marie, and Déjerine. He was highly respected among this group both for his considerable knowledge and for his impeccable manners. He was to make several close friends, among them Sicard. After his appointment to Lisbon the trips to Paris became more frequent. Every year he would spend a period in France and would come back to Lisbon to teach and practice neurology and to devote a considerable amount of time and effort to politics. During the first 15 years of his career in Lisbon, in point of fact, he was much more of a prominent political figure than a prominent scientist. He did write a large number of papers, mostly case reports on several neurologic disorders; and in 1917 he authored a remarkable treatise on neurologic war injuries. Nevertheless, the politician was more evident than the man of research. He was elected more than once to a seat in Parliament and was appointed Minister of Foreign Affairs. He served as Ambassador in Madrid and conducted the negotiations for the reopening of diplomatic relations with the Vatican. In 1918, he was chief of the Portuguese Delegation to the Versailles Peace Conference. His social circle was wide and he entered each new day of political and societal activity with immense flamboyance. The quality of his receptions became legend. Food, drink and style were under his permanent control—he would choose the menus, ponder over the choice of wines, design his wife's wardrobe, and go as far as selecting the uniforms of his personal valet and chauffeur. Gambling was another of his interests and he even wrote a very curious book on the history of playing cards. Personally he was refined without being pompous, somewhat cool but eventually amiable, and capable of momentarily joining other walks of life. It is probable that high office was his goal in the early twenties and that not becoming president of the Republic was a key factor in his dissatisfaction with politics: his public career registered some minor successes which probably did not compensate for the many unsavory aggravations that also came along. Another factor contributing to disenchantment may have been the military coup d'état that in 1926 brought to power a dictatorial regime that put an end to the very liberal democracy that had been his playing field. He chose that precise moment to retire from the political world and dedicate himself solely to research.

Amazingly he was 51-years-old at the time, an age far removed from that considered ideal for someone starting a scientific career. But then again he was not exactly a newcomer to neurologic science: he was, more simply, concentrating on it. Devotion to research came as the alternative to commitment in public life and one may say it arose out of injured pride and frustration. Perhaps it was a second-best inevitable choice motivated by a desire for revenge. And revenge he took. Within a short period in 1927 he had introduced cerebral angiography while keeping much of his social brilliance, which continued to be the backdrop for the scientist as much as it had been for the politican and successful practicing neurologist. But it is interesting to note that the world of make-believe was the counterpart to the caution and attention to detail with which he invested his research.

The achievement of angiography was carried out in very limpid manner. In the way of influences it is probable that Sicard, the inventor of myelography, was all-important. Common to both men was the attempt to improve the diagnosis of the tumors which the advent of neurosurgery had made it possible to treat. The essential concept in myelography—that of using a substance opaque to x-rays in order to reveal the contour of abnormal formations in the nervous system—was also present in angiography.

Moniz decided that if it was possible to produce the opacification of blood vessels, their images would disclose disturbances of a far more informative type than the ones shown by the images of the ventricles in the method devised by Dandy. Moniz expected not only to develop a way of localizing brain tumors but also of predicting their pathologic nature. That the method was a means of collecting anatomic and physiologic data of great importance to the understanding of cerebral circulation was already in his mind at the time. The skillfully planned experiments which led to angiography included the trial of several drugs known to be radiopaque. The reaction of the vessels and of brain tissue was a problem and so was the question of concentration since it could be assumed that too quick a spreading would not permit enough opacity. It was necessary to find a suitable compound and determine the right dose capable of giving good contrast and yet safe enough not to produce blood clots or create emboli. In the course of his own investigation Moniz learned of some previous attempts to inject lipidol into the circulation of limbs and of the complications that followed the injections. This had been done by Berberich and Hirsch in 1923 (1) and by Brooks in 1924 (2). He was well aware of these dangers. In particular iodides and bromides were tested in various concentrations (Fig. 2). He came to favor strontium bromide and sodium iodide as the more probable drugs. Next came the studies in the cadaver by which Moniz first tried to obtain the normal radiologic aspects of carotid circulation. Unlike what was traditionally believed at the time, he noticed there was a definite universal pattern in the carotid branching in spite of the obvious variations from specimen to specimen. He also noticed how much his findings differed from current knowledge related to dissection anatomy. Step by step he developed the technique of picture-taking. Later, the effect of the injection on the blood flow was carefully evaluated in dogs. It took him some time to gather the courage to perform the first injection in man. The early trials, carried out in patients with intractable epilepsy, nondiagnosed brain tumors, and postencephalitic parkinsonism were relative failures, for various technical reasons. One of the patients died shortly after the procedure and the torment provoked by this accident almost drove Moniz to despair. Instead, a month later, he went back to experimenting, reviewing every detail of the work obtained that

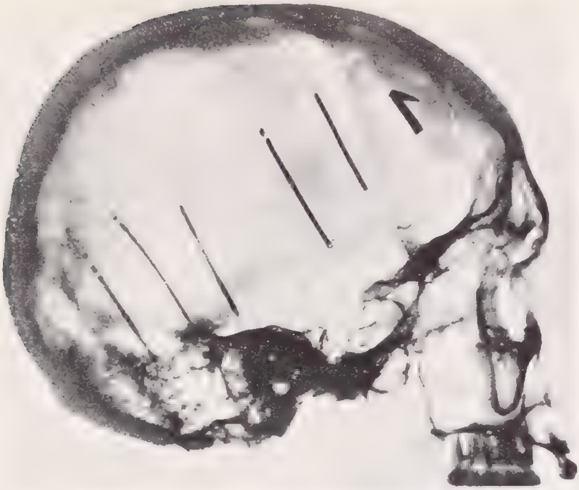

Fig. 2. A skull and a series of rubber tubes filled with different substances, used to study the amount of contrast produced by various compounds against bone tissue.

far and introducing several changes. He finally selected sodium iodide in a concentration of 25% as the contrast of choice and decided on the precise technique for the injection in the carotid (which, at that time, was not percutaneous and required the surgical exposure of the vessel). After painstaking preparation a new beginning was agreed on. Moniz would accept nothing but success.

The description he gives of that very first occasion and of the moment of triumph is one of rare beauty and disquieting emotion. The day was the 28th of June 1927, the place a very modest room in the old University Hospital of Lisbon, and the characters were a patient suspected of a sellar tumor, Moniz himself, and some of his closest assistants, among whom was Almeida Lima, who was to become a famous neurosurgeon and the permanent substitute for the gouty, progressively crippled hands of the master. The result, a mere lateral view x-ray film, was simple and yet full of new information. There was the tumor to be inferred from the distortion of the normal picture of cerebral vessels: the carotid syphon undone, the sylvian arteries compressed upwards early in their course.

A week later Moniz was in Paris. On the July 7 he presented to the Société Neurologique de Paris a paper with the title: "L'encéphalographie artérielle, son importance dans la localisation des tumeurs cérébrales." There was no doubt about its success. Babinski initiated the acclaim, at the end of the session and declared: "...the x-rays Moniz has just shown are remarkable. Every neurologist will have a debt to our eminent colleague for he has obtained a new method to localize intracranial tumors whose seat is so often difficult to determine." Souques ventured that "Moniz has just opened a new path for cerebral vascular research in the living." And Sicard immediately drew attention to the fact "the nonvisibility of one or several cerebral arteries may permit the conclusion that the vessel is obliterated, displaced or compressed;

it will be possible to localize and circumscribe the morbid focus, and in certain cases of brain tumor, otherwise not localized, intervene surgically in the right place. These are the results and we can but congratulate Egas Moniz." Guillain, Roussy, André Thomas all gathered to acknowledge his mastery. The next week Moniz made a more extensive presentation of his work to the prestigious Académie de Médicine, at the invitation of Babinski. He was able to show then the first good quality angiography obtained only a week before, at the time of death of a patient with a right temporal meningioma (Fig. 3). The unoperated patient died and there was a postmortem which became the first case of neuropathologic correlation with radiology (Fig. 4). The paper soon appeared in *Revue Neurologique* in 1927, and he later published extensive monographes in French (*Diagnostique des tumeurs cérébrales et l'épreuve de l'encéphalographie artérielle*, Masson et Cie, 1931, and *L'angiographie*

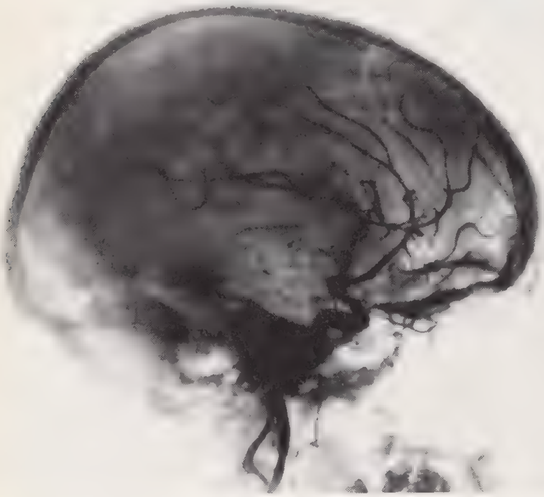

FIG. 3. Angiography of a case of right temporal meningioma, presented to the Académie de Médicine in July 1927.

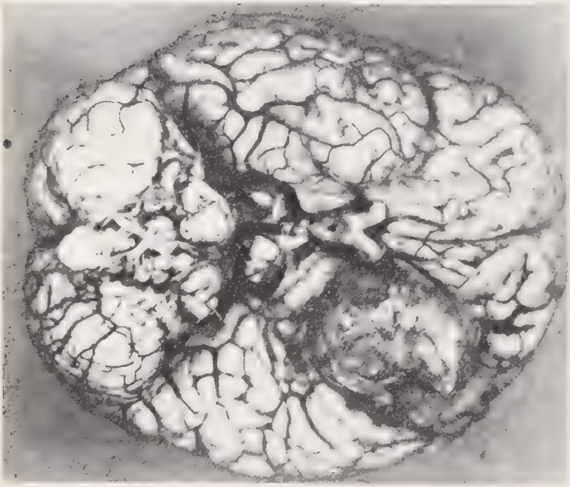

FIG. 4. The brain of the patient referred to in Figure 3.

cérébrale Masson et Cie, 1934) and in German (*Die cerebrale Arteriographie und Phlebographie*, Springer, Berlin 1940). During the thirties, angiography became known mainly through these publications and through the active example of Almeida Lima who became a trainee of neurologic surgery under Sir Hugh Cairns in Great Britain. Surprisingly the method did not become popular until after the second world war, particularly on this side of the Atlantic where it later would be refined and expanded to its present day excellence. This is understandable because in the early days the technique was not without hazards. Also, thorium dioxide, which Moniz favored as the contrast of choice after 1931, was rightly suspected of toxicity. Unfortunately the suspicion was well founded as may be witnessed by the many cases of thorotrast granulomas that developed in some of the radiographed patients.

In 1932 he obtained the first phlebography and stated that the correct angiographic examination should include bilateral visualization of the vessels in the arterial and venous phases of circulation. He was the first to obtain angiograms of aneurysms and angiomas and he was thrilled to identify the picture of carotid thrombosis relating its degree and localization to the clinical symptoms and to the pathophysiology of brain circulation. He also performed the first complete studies of cerebral circulation by injecting thorotrast into the subclavian arteries and made a careful radiologic description of posterior fossa vascularization. He identified the pictures of the more frequent neoplasms and enjoyed writing on what he coined the "carotid syphon." He also insisted on the point that there was not a middle cerebral artery but, most frequently, a group of two or three middle arteries which he named "sylvian arteries" and "sylvian group." Even if Moniz did not live to see all the advancement and expansion of his method he did foresee much of its latter day progress and he permanently introduced changes that made the technique simpler and safer. He was proud of the fact that, already in the forties, ambulatory patients could walk home on the very day of angiography with no visible risk and no major complaints. The quality of his description of abnormal ateriographic and phlebographic patterns still fascinates students acquainted with his writings.

Of no lesser relevance was the fact that cerebral angiography paved the way for angiography of other sectors of the human vascular system. Soon, friends and associates of Moniz were trying to visualize other vessels in the human body and Reynaldo dos Santos, at the time a professor of Surgery in Lisbon, performed the first aortography and kidney angiography while Lopo de Carvalho and Hernani Monteiro performed, respectively, angiopneumography and lymphography. Moniz had initiated the "Lisbon school of angiology" as it came to be called during the thirties and forties. Had this been his only endeavor in the field of research his decision to concentrate on it would have been amply justified and, presumably, his political frustrations quenched.

However, by the middle of the thirties, Moniz had again decided to open a new avenue in science. This time the project was even more audacious. The enterprise involved some danger and it was clear from the start that controversy of a religious, philosophical and social nature would certainly arise. Courageous enough not to consider any of these implications, Moniz was firmly decided to design and carry out a surgical procedure to interfere with deviant behavior and treat some types of mental disease. In December 1935 the first leucotomy was performed in Lisbon in the same place where angiography had been born and by the very same hands.

In a way the two discoveries are closely related. Thus even if both have opened a possibility of research into the physiology and pathology of the nervous system, one feels that the real aim behind them was in the field of applied medicine. Diagnosis leading to better therapy in one case, and therapy in the other, were certainly the main considerations for Moniz. Angiography responded to the plea of the undiagnosed patient with intracranial expanding growth and was an urgently required development in view of the advancement in neurologic surgery. Ventriculography was simply not enough in terms of semeiologic information. Leucotomy mainly responded to that most quizzical disease of human medicine, schizophrenia, and was an attempt to modify behavior long before the advent of effective medical therapy. The pragmatic goals and boldness of both projects bring them together as parts of a consistent pattern. But the resemblance stops there because a consistent methodologic difference distinguishes the two works. Angiography could be prepared experimentally in a laboratory setting where risk was progressively minimized before the final application to man was decided. Leucotomy, on the other hand, was designed on the basis of a particular theoretical model of brain/behavior relationships, which at the time, and probably still today, was impossible to test in the laboratory: the procedures had to take place, right from the start, in the sort of human being they were aimed at. It took cold blood to go ahead.

Moniz has never given a definite account of all the influences leading to leucotomy. I suppose the work of Jacobsen and Fulton at Yale (3) concerning tha ablation of the frontal lobes in the chimpanzees Becky and Lucy should be regarded as a major influence. Both animals had been trained to do several learning tasks, such as delayed reaction tests and problem boxes. Then they were operated on the same date and areas 9, 10, 11 and 12 of Brodmann's reference were ablated unilaterally. No change was noticed. Three months later the same operation was carried out on the other side and after that some subtle change was produced. Apart from the fact that some of the tasks could no longer be performed, the most remarkable feature concerned the emotional behavior of the animals. The animals seemed to have lost their sense of frustration and would not react aggressively when punished. They seemed devoid of emotional expression and were indifferent to their own failed performance. They were as careless and happy as if, as Dr. Jacobsen put it, "the animals had joined the happiness cult of the Elder Micheaux and had placed their burdens on the Lord." Moniz obviously knew of their results for he was in London in the room where they were first present, at the 1935 World Congress of Neurology. At the end of the meeting, according to Fulton's own description "Moniz arose and asked why would it not be feasible to relieve anxiety by surgical means? At the time," Fulton continues, "we were a little startled by the suggestion, for we thought that Dr. Moniz envisaged a bilateral lobectomy which, though possible, would be a very formidable undertaking in a human being" (4). Nevertheless that was not the trigger for his interest. For quite some time before he had been vividly concerned with a paper by Brickner, a physician at the Neurological Institute in New York, published in 1932 (5) where this author described a long study of a patient in whom Dandy had removed most of both frontal lobes. After a relatively long postoperative period during which he lost his spontaneity and behaved in a childish way, the patient progressively recovered his higher faculties. Later on he had no dramatic memory loss, he retained his ability to write and draw, could speak fluently and understand speech, and could even go on playing checkers. As to the man's personality there were some neat changes. He had been a shy, passive, introverted, character, and had now emerged as a more open minded, vivacious, even boasting person. Brickner's description of the modification of behavior coupled with what then looked like a scarcity of major neurological symptoms may indeed have influenced Moniz—regardless of the fact, later known, that the pathology of Brickner's case was much more extensive than was suspected. Fulton himself is convinced Moniz "had considered surgical interference (with some of the more severe psychoses) long before hearing of our results." I think it is fair to say the concept had been there for a long time and that Brickner and particularly Jacobsen and Fulton probably gave Moniz the minimum theoretical support to proceed.

The essentials of the theoretical model behind leucotomy concern an extensive knowledge of the anatomy and physiology of the time and a "reflexological" attitude towards psychology. His concept of the brain/behavior relation was supported on the one hand by Cajal's theory of the neuron and on the other by the work of the Russian school of psychology from Sechenov to Pavlov. Moniz was also convinced of the importance of the frontal lobes as the seat of structures governing higher nervous function and not ascribed to any form of instrumental nervous operation like sensory input or motor activity. Moniz was the organicist par excellence and he clearly conceived psychiatry as a kind of desert soon to be invaded by neurology. He viewed mental activity as dependent upon nervous circuitry. Accordingly, mental disease stemmed from pathologic functioning of nervous nets and its treatment should be planned along the lines used for neurologic disorders. Although his approach was sometimes crudely mechanistic it was not unlike that of a present-day cybernetician. He thought, for instance, that ideas were linked to a certain circuit or set of circuits which tended to become fixed by conditioning. Delusions or obsessive-compulsive traits of behavior were the product of wrongly formed circuits or connections, and their resistance to sound reasoning and verbal therapy was the result of a rigid fixation in the way impulses traveled. Hence his rather simple but promising idea that by disrupting the aberrant circuits one could disrupt the correlated deviant behavior. And if circuits pertaining to high-level concept formation and emotional regulation were articulated in the noninstrumental frontal lobe, it was predictable that by surgically undercutting its white matter connections to other parts of the brain it was possible to destroy the ill-producing connections and restore the lost balance. In his memoir he confides: "The destruction of cellular connections in the brain of mental patients in order to alternate the currents that cross them, finding new paths for them, was a conception that in view of its fundamental organicism was not well accepted by those that choose the meandering of psychopathological dialetics bordering on methaphysics. Only to Almeida Lima did I trust the secret of my aspirations and speculations and we kept the matter secret" (6). Convinced that the operation would produce little harm he tried several techniques for the destruction of white matter pathways to the prefrontal areas. Subcortical alcohol injections were used first but later he had Almeida Lima designed the "cerebral leucotome," a small instrument capable of producing wide undercutting with a relatively small lesion of the overlying cortex (Fig. 5).

The first operations were a considerable success in spite of the difficulties. The patients chosen for surgery were long-term schizophrenics, depressives, or obsessives, suffering intensely at a time when there was no effective medical means of helping them. In this context—and in this context only—it is possible to say that leucotomy was a welcome addition to therapy regardless of how complicated and controversial. Anxiety was certainly reduced in 16 of the first 20 patients. The agitation that made most of them so difficult to manage in a hospital or home environment was also diminshed. And in seven cases both obsessive and delusional symptoms did seem to vanish, giving way to a possible adaptation to reality. Encouraged by this, in 1936, Moniz made the first international presentation of the results of the first twenty cases (7). In

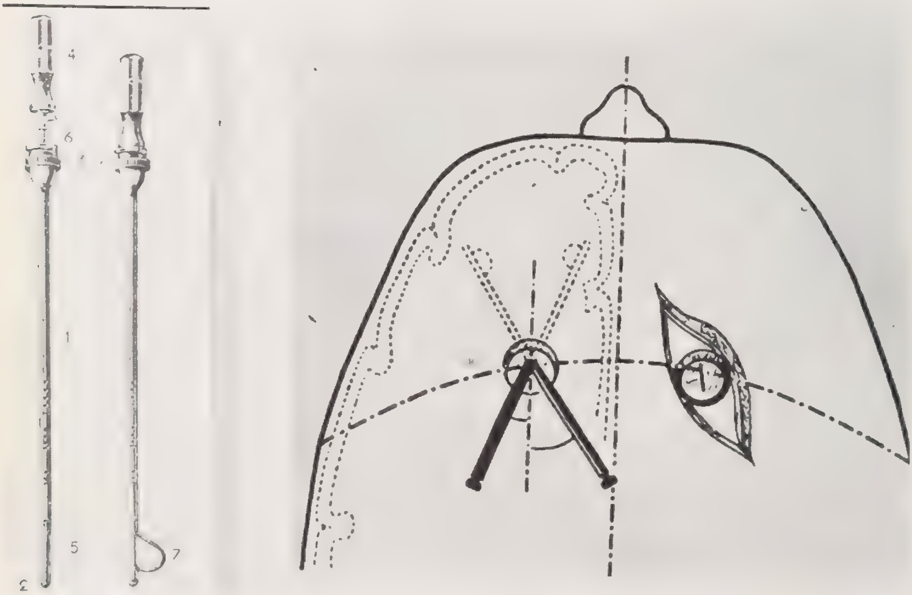

FIG. 5. The original leucotome, a blunt needle with a stilette that bulged laterally when pressed from above. When rotated the instrument produced a circular cut in the white matter. The picture shows the point where the burr holes would be made and the direction with which the leucotome was introduced.

this he stated that seven were very much improved, another seven were ameliorated, and in six there had been no change.

In the epic days that followed these first reports, I think Moniz was never able to make a clear weighing of the advantages and disadvantages of leucotomy. He and his close associates were carried away by this new opportunity of actually determining some therapeutic benefit to otherwise condemned patients. One feels that they were prone to dismiss or ignore the important neuropsychologic deficits induced by the operation while highlighting the obvious amelioration. In Almeida Lima's skillful hands, it is true, there were never major neurologic deficits. However, this was not enough to make the procedure more acceptable or less debatable, and one really has to think of the many thousands of persons with uncontrollable anxiety or intractable pain that found relief in leucotomy, to consider that the whole enterprise was fully justified. The worldwide reaction to leucotomy was varied. In North America, for instance, it immediately found a following and soon Watts (8) was developing the method and creating lobotomy (Fig. 6). One is, in fact, astonished that there was not more widespread reaction against a therapeutic measure whose scientific foundation was somewhat fragile and might even have questioned religious and philosophical beliefs. Leucotomy, or lobotomy, involved traumatic, unrefined procedures that for the layman and for many a doctor seemed more like mutilation than therapy. Eventually however, controversy started. The crude, indelicate way with which some surgeons approached and practiced leucotomy contributed to the reaction. Yet, even at the peak of criticism the scientific community was divided and tended to support the method rather than fight against it. This is clearly shown in the fact that the 1949 Nobel Prize was awarded for leucotomy and angiography was practically ignored.

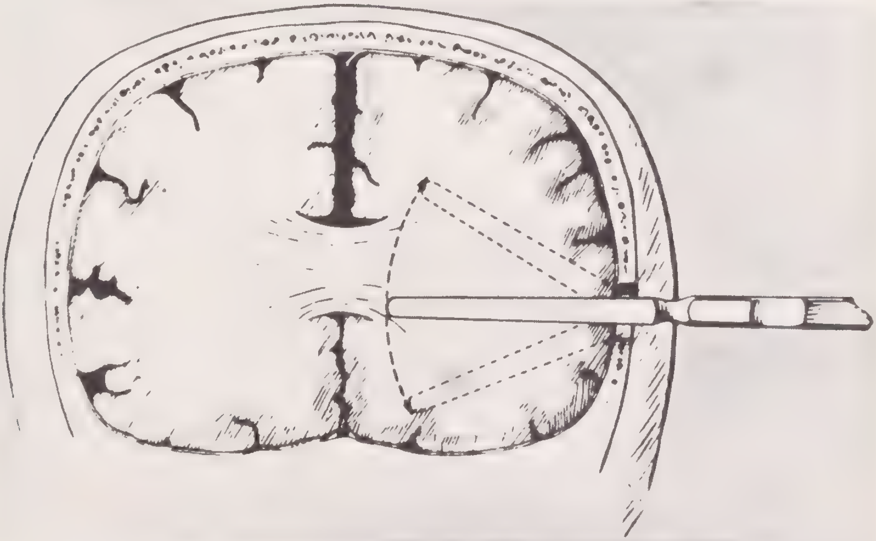

FIG. 6. The lobotome of Freeman and Watts and the point where it would be introduced.

Because of all the social shortcomings, it took some decades before leucotomy found its proper setting within the neurosciences. Today it is included in a branch of studies and procedures that go under the unfortunate though expressive designation of psychosurgery (psychosurgery is really a misnomer; leucotomy is neurologic surgery applied to mental patients). Leucotomy is now finding its proper place within the framework of the neurology of behavior in a truly multidisciplinary perspective that I imagine was the one intended by Moniz. Stereotactic techniques, along with the development of neurophysiology and the development of neuropsychology, have recently given rise to a very important group of studies on the so-called "fractioned leucotomy." The amount of information that is now being collected from these studies as well as the very good clinical results of these procedures are, at last, giving to leucotomy the image Moniz wanted it to have when he invented it. If the future will confirm this is a fertile track, one may certainly speak of leucotomy as a concept and as an approach that came too soon for the technology and medical philosophy of its own epoch.

Moniz retired in 1944. If he had been younger and had more resources we would probably have seen the development of a third major work from him: efficient surgery for parkinsonism which he had been thinking of and practicing during the thirties. Most of his notes on the surgery of parkinsonism are unpublished except for a paper in 1941 in the Swiss journal *Chirurgie* (9). It is interesting to note the obvious connection between leucotomy and surgery for parkinsonism. They both represent a high point in terms of a therapy devised on the basis of a very mechanical, physical, prechemical concept of the nervous system. They stemmed from turn-of-the-century physiology and philosophy and they were supported by the development of neurophysiology and technology. And their role in the medical sciences has been somewhat transformed by the development in the fields of chemistry and pharmacology which brought neuroleptics and dopamine to the forefront.

In 1955 Moniz died at the age of 81. At home he continued to write, mainly essays on history, on the arts, and literature. And he appeared daily in his office, ready to view and comment on the angiograms of the day—all this, in spite of the pains and suffering resulting from his uncontrolled gout. He was always full of new ideas which he expected his one-time assistants to appropriate and develop. There were too many brilliant hypotheses and too few people or technical means to keep up with them. He maintained his kindness and commanded the same veneration from people around him, even from his successor, António Flores, a very gifted, cautious, scholarly neurologist who would rather learn about new facts than discover them and, accordingly, was critical of Moniz's ventures into the unknown. Moniz practiced to the eve of his death and was, by then, obviously content with himself.

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Cloud Nine Academe and the Trenches of Health Administration

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The peculiar chemistry of New York City itself, the on-the-job imperatives of its Health Department, the jealous vigilance of public health advocates have periodically combined to endow the top ranks of the New York City Health Department with more than a statistically random sample of professional excellence and social devotion.

George James epitomized such leadership. His stature and influence transcended the geographic jurisdiction of the Department. His papers continue to read well today. His espousal of rational structuring of health care delivery, of geriatric services, of maternal and child health care, of prison health services, of family planning services, of fluoridation, of nutritional services, of environmental protection, etc., etc., provide an explicit public health agenda for us all.

Gratefully, then, do I acknowledge the honor of being selected as the first annual speaker of the George James Memorial Lecture. I interpret this selection as a command from the colleagues of Dr. George James to reconstruct and to reprofessionalize our Health Department so that it may regain the luster it once projected under the first deputy commissionership and commissionership of the public health giant whose memory we honor today.

I shan't mesmerize you today with statistics. Instead I bring you biased and suspect personal perceptions from a career that so far has oscillated like a pendulum between the theoretical and the applicative. Most recently, for example, I have fled from the earnest nuances of faculty meetings to seek refuge in the goldfish bowl of the New York City Health Commissionership.

Specifically I am asked to squeeze some intellectual nutrients from that perennial chestnut—how formal education in health administration is supposed to relate to the real world of health administration. In short, I am to try to reconcile the abstractions of Cloud Nine Academe with the messy splatter of the trenches. What are some observations that we can abstract from the past decade?

Observations

(1) The rhetoric that trademarked the self-styled political health activists of the late 1960's and early 1970's has ceased to beguile even those with sympathetic leanings. It has proven easier to sloganeer than to master the

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administrative skills that derive from a knowledge of biostatistics, finance, health economics, accounting, epidemiology, environmental health, and the imperatives of health administration.

(2) The aforementioned political health activists achieved power by applying the special political skills that tapped the passions of the late 1960's. Fashions in passions change—even in health administration. Political skills once relevant enough to wrench jobs from an Establishment resigned to buying off nuisances by giving out jobs have become anachronistic in an age of debunking, deromanticization, and "stagflation."

(3) Rhetoric notwithstanding, on the job these political health activists proved to be tame pussycats when confronted with the actual sociopolitical and economic constraints of health administration. There were few of those great leaps forward originally promised or threatened if and when these activists came to power.

(4) In view of their negligible educational and experimental background in health administration, it was no surprise that many of these political health activists flopped on the job.

To the cognoscenti their technical inadequacy was obvious, of course, from the beginning. But now the news of their inepititude has begun to filter down as well to the increasingly disaffected fellow ethnic and socioeconomic class they purport to serve. Political health activists with a poor administrative track record are in the process of being identified and rejected by the ethnic and socioeconomic class that brought them into power in the first place.

(5) Ten years ago there was a paucity of representational ethnics with technical skills. They are now being produced with increasing rapidity. Graduating from graduate schools that teach health administration is a new breed of health administrators, bearing not only appropriate ethnic and ideologic credentials but formal educational qualifications as well.

(6) In an effort to discredit these competitors for their jobs, the old guard political health activists (a) routinely disparage formal education in health administration and (b) accuse the new breed of ethnic self-hatred, treason toward their own class, and co-optation by a malevolent and Machiavellian Establishment.

My thesis is simple. It is in the interest of competent health administration that the new breed of health administrator receive encouragement and increasing responsibility under the best professional supervision. With adequate experience as well as education, the new breed should be able to displace the political health activists by 1980. The new breed will be no token representation of ethnicity and socioeconomic class, if measured by ability to achieve desirable social goals. The new breed paradoxically will be more activistic than the political health activists whom they will have displaced. They will shout less and will use less salty language. They will accomplish more.

Now let us turn to our subject. We have an immediate problem. Health administrators have historically been afflicted with self-denigration, if not self-contempt altogether. A dysfunctional status gap has traditionally yawned between the clinical practitioner and the health administrator with the Masters degree, whether or not the health administrator possesses the medical degree (1). Historically, most clinical practitioners have tolerated the health administrator as little more than a glorified manager of hotel services. Someone, after all, has to make certain that hot food is delivered to the patient on time and that the sheets are clean. Worse, over the years, the health administrator has tended to view himself in a similar way. However, a fundamental change is underway. At present the relative status of practitioner and administrator is discernibly shifting to reflect the newly evolving realities of professional responsibility as the health administrator increasingly immerses himself in quality and cost control activities. There is a major shift in bureaucratic power as well. To be sure, the American Medical Association growls occasionally in nostalgic remembrance of times when it terrified government and practitioners alike. But the informed are aware that the AMA has been reduced almost to the status of a toothless, clawless tiger. In contrast, the American Hospital Association, the organizational spokesman of one group of health administrators, grows more powerful daily. Clinical practitioners at last are beginning to acknowledge ruefully that hospitals are more apt and are more capable of exercising tyrannical control over the professional lives of clinicians in the short and long run than the government that they have steadfastly feared over the years. In any event health administrators and health administration are finally coming into their own.

Skills

Why should I feel called upon to polemicize on behalf of the importance of teaching technical skills? Certainly no clinician of intelligence refers to technical skills as superfluous. There is no moral way or immoral way to prescribe cardiac glycosides, diuretics, or antibiotics. There is only a correct way or an incorrect way. In contrast, self-styled political activists in health care administration give the impression at times that they but grudgingly concede the utility of technical skills at all. We live in a world of egalitarianism gone mad, where special knowledge is deemed superfluous and sometimes suspect, for special knowledge is damned as the means the imperialistic professional has customarily used to mystify and oppress the masses throughout history.

There's nothing to it. As the recent best seller demonstrated, anyone can be his own probate attorney. As the recent *Village Voice* articles have pointed out, any woman with technical equipment cum ideology can scrutinize her own uterine cervix and thereby save paying a fee to an overpaid, arrogant, exploitive, insensitive male chauvinist pig of a gynecologist. This is the age of cookbook do-it-yourself paraprofessionalism. This is also the age of the put-down, for the extra fillip is to expose most professional expertise for the pretentious nonsense it allegedly is.

Well, obviously if we can level the lawyer and the gynecologist, if we really can paraprofessionalize most professional activities, then surely the health administrator is even more susceptible to leveling. His vulnerability can be summed up in two sentences excerpted from 100 conversations I have had with the people or those who purport to speak for the people: "The key thing, man, is to be able to relate to the community. We can always hire the experts when we need them." One runs into the same attitude expressed in the more elegant language of faculty meetings. In 1972 I participated in one of my first faculty meetings at Columbia. I had previously vowed to myself to keep a low profile until I learned the mores of my new environment. My academic colleagues were discussing the criteria of admissions. I had already been assigned to the Admissions Committee. Evidently my attitude about which students ought to be admitted had reached some of the general faculty. One senior member of the faculty challenged my viewpoint in more or less the following words: "I understand, Dr. Bellin, that you are insisting on academic distinction on the part of all candidates to be admitted to the School of Public Health." He continued: "As for me, if I had to choose between a candidate with academic distinction but poor social commitment, and a candidate with less academic distinction and more social commitment, I would choose the latter."

Note the inverse correlation. Presumably this view would hold that membership on the Dean's List statistically connotes indifference to human suffering, if not cruelty altogether. One wonders. Are we really to assume that the selectivity of graduate schools is so limited that it is impossible to recruit future health administrators both with brains and compassion? I assert that there is no need to compromise. Future health administrators are available with both—and they come in all colors, ethnicities, and socioeconomic classes.

But there is another reason for the denigration of administrative skills. There is a popular thesis in this country that almost anyone with minimal intelligence can become either a teacher or an administrator. One would imagine that the cognitive dissonance emanating from OEO, Model Cities, Medicaid, Medicare and 314e by now would have shaken the faith of the most obstinate believer in this doctrine. The view persists nevertheless. Consider the conversation I had with Professor X, the head of one of the academic divisions of the Columbia University School of Public Health, shortly after I was appointed Professor and Head of the Division of Health Administration there. A candidate for a degree in his division had turned out to be mediocre and worse. Professor X suggested to me that under the circumstances perhaps the student in question might do better by transferring to my Division and becoming a health administrator. The assumption was clear. Having flopped in presumably the more intellectually demanding field of a basic public health science like biostatistics, epidemiology, ecology, population control, or medical sociology, the student was possibly qualified for the allegedly less academically rigorous world of health administration. To myself I could not but speculate how puzzled if not indignant Professor X might be if I were now to suggest the transfer of some of my own academic lemons to his division instead.

To be sure, a student who does poorly in one field may indeed perform splendidly in another. But Professor X's manifest attitude about health administrators and the educational process that grinds them out reflected a common view that administration is basically common horse sense, getting along with people, and the like. It's not as if you have to master complex calculus, metabolic cycles or biophysics. Anybody, or almost anybody, including dropouts from tough academic programs, ought to be able to make it in health administration. After all administration is an art, not a science. This devastating cliche is advanced whenever one advocates the teaching of intellectually rigorous skills to future health administrators. Well, so is medicine an art—and the ministry an art, and law an art—that is, each of the learned professions is an art. Most human activities are arts, if by art we mean the subtle application of special skills. The special skills of administration are wholly teachable; the subtle application of these special skills, at least partially so.

For years I have insisted that the so-called good guys have mainly themselves to blame for the extent to which socially indispensable programs under public auspices have been discredited. Progressives have blamed unpopular ideology as the culprit. They are dead wrong. It is not unpopular ideology. It is bad administration. Recall that without appreciable public support in the beginning these programs could never have been funded and implemented by government in the first place. No, it is a cop-out to attribute the loss of support to some kind of belated popular revulsion against the social objectives of these programs. What really happened was that the minority in opposition stayed alert and seized on the sloppy management of Model Cities, OEO, Medicare, Medicaid in order to rally the lukewarm adherents and uncommitted population. It was relatively easy thereafter to discredit each of these programs themselves. It is worth recalling that meeting the payroll was never supposed to be the exclusive preoccupation or achievement of the political right.

Just as the Devil can quote scripture, so can the klutz in health administration parrot the OK phraseology of the day—the desirability of continuity of care, the perniciousness of copayment, the fragmentation of services, the nonsystem of service delivery, the pervasiveness of the national health-care crisis. We possess a remarkable tolerance level to a kind of verbal glop that has supplanted insightful analysis. Talk is cheap. After a while the same slogans repeated and repeated and repeated anesthetize and cease to communicate meaning. Rhetoric has become the opiate of many of the alleged change-agents of the health field. "Medical care—a right not a privilege" becomes an empty slogan on the lips of orating managers who blunder and blunder—and blunder again—as they misallocate scarce resources, as they keep inadequate books, as they lack the capacity to exercise elementary political skills, as they fail to identify and frustrate the inevitable opportunists with their concomitant rip-offs. In the real world technical skills and social values are indispensable. In order to prepare the future health administrator to function competently in the real world, a graduate school curriculum ought to teach technical skills without denigrating social values and ought to teach social values without denigrating technical skills. In the real public health world of finite resources and infinite social objectives, the value system gives priority to the social objectives to which these finite resources under the partial control of the health administrator will be allocated.

Elsewhere (2) I have detailed the functional inadequacies of health administrators and the educational inadequacies of the graduate schools that have produced them. Consider, for example, the question and accompanying comment of a graduate newly minted from one of our well-known schools of public health. "Dr. Bellin, is this Health Department involved with politics? Because, if it is I don't want to work here." This was a novice poised to enter the field of health administration and presumably near the peak of his intellectual prowess, if as yet unencumbered by professional experience. Education had failed to shake his awesome naivete. Reality would yet have to inculcate such administrative truisms as: (1) what is taught in high school civics is but the smudged reflection of the mechanics of actual government; (2) sophisticates in government do not use the term 'politics' as a pejorative; (3) in human society decisionmakers have but two methodologic alternatives—(a) the political process, i.e., "politics," or (b) physical violence. The political process remains preferable. People who practice the political process with skill are called politicans.

The rest of the interview suggested that his school should have prepared him better. He was by no means unique. Most of the young men and women I interviewed not only knew little about the sociopolitical world of public health but even less about health economics, health insurance, accounting, finance, operations research, quality and cost control of health services, and the other skills I argue that a modern health administrator should master beyond an introductory level.

Subsequently, when I joined the faculty of the Columbia University School of Public Health as Professor and Head of the Division of Health Administration I declared war on the 9-month masters degree. At faculty meeting after faculty meeting, I characterized this degree as debased. I gathered a cadre of allies about me. Our cadre expanded the 2-semester requirements for the masters degree to a minimum of 3 semesters. We went further. We developed two 5-semester programs—a joint program of the School of Public Health with the Graduate School of Business, leading to an MPH-MBA double degree and a joint program of the School of Public Health with the School of Architecture and Urban Planning, leading to an MPH-MS (urban planning) double degree. We made compulsory a supervised residency up to one year in health administration and tacked on a masters thesis requirement as well. The graduates of these joint programs from Columbia possess skills that put them into a totally different dimension from former Columbia alumni and most of their competitors in health administration from other American graduate schools.

The Mr. Chips Syndrome

In teaching administrative skills faculty must beware succumbing to the Mr. Chips Syndrome. Teachers of health administration seem particularly vulnerable. The Syndrome bears the following recognizable signs and symptoms: (1) Teachers begin to give lectures that consist primarily of their own war stories. The tales grow better from course to course with the lecturer cast predominantly in the role of hero; (2) The teacher's mental fix remains tied to the last time he worked in the real world. But, of course, as time goes on, this real world fades more and more into the past. There is increasing remoteness and irrelevance; and (3) The teacher begins to cultivate delightful eccentricities that become the stuff of affectionate "old boy" anecdotes. I submit that the volatile and impermanent field of health administration cannot afford such lovable types in health administration academe no matter how much quaintness and cuteness they radiate at annual alumni meetings. The Mr. Chips Syndrome may be tolerable in the departments of Latin where neither the ablative absolute nor the subjunctive have changed appreciably during the past two millenia. The Mr. Chips Syndrome is unacceptable in departments of health administration. It is not enough for health administration professors to pontificate before class after class of awe-struck students. Graduates in health administration should not be allowed to escape from school with their masters degrees intact without intensive exposure to contemporary working health administrators whose wounds are still open and raw.

We can vaccinate our faculty against the Mr. Chips Syndrome. To do so we are obliged to introduce the following policies: (1) Teachers must periodically go on leave from their teaching positions and take jobs in the real world of health administration; (2) Teachers must routinely act as consultants in health administration. These responsibilities would compel them to consort under fire with the troops in the field even while they are professors; (3) Teachers should always continue some kind of operational responsibility for a health enterprise. Running something subjects one's theories and avocations to continuous reality testing; and (4) At the same time full-time health administrators, whether public health officials or employees of health enterprises, should be required to teach on a part-time basis. This will further cultural interpenetration between the real world and academe. Of course, what I am recommending is precisely the model that has worked so well over the years for people who teach clinical medicine in medical schools or at hospital centers. These teachers continue to see patients at least on a part-time basis in order to keep their clinical hands in. Similarly, health administrators, whether on faculties or on jobs, must always keep their administrative and academic hands in.

Values

I take you back to Springfield, Massachusetts—to the year 1963. Curiously enough the problems facing the Health Commissioner of Springfield, Massachusetts are generically identical to the problems facing the Health Commissioner of New York City, although with less than one-fiftieth the population and budget. While Health Commissioner in Springfield, Massachusetts between 1962 and 1966 I encountered a form of aggregate behavior typical of some local medical societies. I tried to persuade my colleagues in practice to support a public health program of mass Sabin vaccine immunization. The leadership of the local society opposed the program. This was the same medical society that had refused to cooperate with the health commissioner who had preceded me when he had tried to launch a mass Salk vaccine immunization program. Only when I threatened to go it alone and publicize the reason for my going it alone without the suport of the medical society did my colleagues agree to support the program. Also in Springfield I ran into similar medical society resistance when I promulgated two programs: (1) mass tetanus immunization for the City's policemen and firemen and (2) citywide glaucoma screening. So angry once were some of my colleagues that a group of school health pediatricians banded together in an ad hoc organization and went to see the Mayor to protest against my allegedly aggressive behavior with respect to the number of hours they were expected to work each week.

Each time a similar message was communicated to me: in their view my job as Health Commissioner was confined to providing "health education" to the public. "Health education" they defined as success in persuading the public to go to the offices of private practitioners to receive Sabin vaccine, or tetanus inoculation, or glaucoma screening on a fee-for-service basis. Any other activity, in their view, represented an unwarranted incursion by the public health agency into private practice.

Assume that the public health professional not only has been taught his appropriate role but moreover believes in the validity of this role. Should a school of public health then try to inculcate the principle that the public health professional be prepared ultimately to lay his job on the line if and when necessary in order to play such a role with moral verve? And, if so, how does the school of public health inculcate the necessary values? To work in an atmosphere where his self-perception as a public health professional normatively differs from the role assigned to him by his practicing colleagues requires that the public health professional be taught his appropriate role. Moreover, he must believe fervently in the legitimacy of this role. This is often difficult because he will always be in the minority. The marginality of the public health professional has been commented upon in the literature (3). To sustain himself the public health professional needs more than an annual meeting of the APHA or AHA where he can become spiritually refueled for the next 12 months. He needs values. To the major extent he will bring those values with him to graduate school. It is a trifle late for the graduate school in health administration to teach him a value system that is ordinarily grounded in the religion and ethics taught throughout childhood and adolescence in the home. But certainly the graduate school should build on the values he brings with him. There should be appropriate role models on the faculty with whom the novice can identify. Medical students become internists or surgeons or radiologists or anything because fortuitously they were exposed to some such members of the faculty who inspired them. If we want skillful, socially committed health administrators, then we need health administration teachers on the faculty who demonstrate skill and social commitment in their daily professional activities.

Final Comment

Colleagues, there is a lot riding on our ability to reconcile the abstractions of Cloud 9 Academe in health administration with the messy splatter of the trenches in health administration. The direction national and local health policy ever takes always comes from the people who are "there," i.e., the people who are positioned in strategic locales in governmental and private health bureaucracies. These people are rarely clinicians in private practice. They are the health administrators who have been and will continue to be produced by the combination of school and apprenticeship techniques of education. Whatever else the unprecedented events in health affairs of the past decade have taught us is that our field is famished for health administrators of technical excellence and substantive devotion. As we consider the past decade we must confess to dissatisfaction with our accomplishments. In the spirit of the late Dr. George James, let us, his successors, strive to do better.

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Twin Gestation*

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In 1958, Doctor Guttmacher and one of the authors reported on 1,327 twin deliveries occurring among 117,764 deliveries (1.13 percent) from the Obstetrical Statistical Cooperative. (1) The present report is from the Cooperative for the years 1961–1972, during which interval 601,299 women were delivered of 6,503 sets of twins, an incidence of 1.08 percent. The patients were delivered in 32 different hospitals and the number of years in which an individual hospital contributed to the study varied from one to twelve years. The number of sets of twins from a single institution varied from 33 to 1,031.

The main weakness of any study so conducted is the inability to consult the individual hospital recorded. The main strengths are the large number of cases and the common recordings. Also, the contributing hospitals cover a wide spectrum of institutions, from large university and/or municipal hospitals to medium-sized voluntary hospitals. This pooling gives a better estimate of practice than is achieved by analysis of individual hospitals.

Birthweight in multiple pregnancy

Birthweight is associated with the rate of growth in utero, the duration of gestation, and litter size. McKeown and Record (2) reported the mean birthweight of single fetuses to be 3,377 grams and the duration of gestation to be 280.5 days; twins, 2,395 grams and 261.6 days; triplets, 1,818 grams and 246.8 days. Our data (1) revealed that for comparable weeks of gestation the median weight of the single fetus is 200 to 800 grams heavier. Birthweights are significant only in relation to period of gestation. Table I reflects the average weights of twins by the types of combinations and sequence of birth.

The average weights reported here are smaller than those reported elsewhere, because we have included all sets of twins in which at least one fetus weighted 500 grams or more. If the fetuses of under 29 weeks gestation are not considered, the average weights would be as follows:

M/M		F/F		M/F		F/M	
A	B	A	B	A	B	A	B
2,368	2,326	2,322	2,283	2,475	2,322	2,327	2,425
A − B = 42		A − B = 39		A − B = 153		A − B = −98	

The like-sexed pairs show that the first-born is about 40 grams heavier, on the average, and that the male pairs are heavier. In mixed-sex pairs, the male is heavier. When the male is second born, the weight difference is about 100

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grams, but when the male is No. 1 the difference in male/female weight is about 150 grams. This is the weight that would be gained by the female after two additional weeks in utero.

The first infant, in general, is heavier than the second, except in the female/male pairs where the male's mean weight exceeds the first infant's (female) by 95 grams.

Length of gestation

The median duration of pregnancy is similar for the various sex combinations (Table II). Twin-gestation infants appear to gain weight, as do singletons, in an increasing amount each week except that the fall-off appears earlier. Table III demonstrates a progressive weekly increase until the 34th week when the peak gain of about 200 grams per week is reached. After the 34th week of gestation, the rate of weight increase recedes, and after the 42nd week of gestation a loss of weight is observed for each continued week in utero.

Duration of pregnancy

The relationship in birth weight among the sex combinations is interesting (Table II). It might be expected that the male/male sets would have the heaviest average infant birthweight, but this is not so. The mixed-sex sets

TABLE I

Birth Weight in Grams

Gestation (Weeks)	M/M		F/F		M/F		F/M	
	A	B	A	B	A	B	A	B
20 or less	604	614	417	800	464	450	333	383
21–24	691	691	693	682	650	607	560	720
25–28	997	989	934	947	1,170	1,083	985	1,013
29–32	1,540	1,530	1,465	1,499	1,547	1,478	1,419	1,521
33–34	1,899	1,922	1,866	1,858	1,964	1,839	1,899	2,059
35–36	2,206	2,183	2,129	2,110	2,289	2,174	2,134	2,246
37–38	2,518	2,457	2,431	2,369	2,548	2,441	2,438	2,560
39–40	2,712	2,632	2,626	2,574	2,808	2,587	2,688	2,774
41–42	2,714	2,688	2,776	2,743	2,940	2,740	2,727	2,716
43–44	2,753	2,828	2,630	2,521	2,835	2,505	2,719	2,727
45+	2,350	2,283	2,630	2,550	2,950	2,800	2,700	2,950
Unknown	2,106	2,102	1,922	1,900	2,289	2,111	2,172	2,195
Total	2,267	2,228	2,249	2,214	2,411	2.261	2,235	2,330

M/M = Male/Male; F/F = Female/Female.

TABLE II

Duration of Pregnancy and Birth Weight

	M/M	F/F	M/F	F/M
Median Duration of Pregnancy (Weeks)	36.7	37.0	37.0	36.8
Birth Weight (Grams)	2,248	2,231	2,336	2,283

TABLE III

Weight Gain by Duration of Gestation

Gestation (Weeks)	Average Weight (Grams)	Gain in Previous Period (Grams)	Weekly Gain (Grams)
20 or Less	523	—	—
21–24	679	156	39.0
25–28	994	315	78.8
29–32	1,505	511	127.8
33–34	1,902	397	198.5
35–36	2,174	272	136.0
37–38	2,460	286	143.0
39–40	2,658	198	99.0
41–42	2,748	90	45.0
43–44	2,688	–60	–30.0
45 or more	2,669	–19	–9.5

actually have the heavier fetuses. The sequence is male/female, female/male, male/male and female/female. In the mixed-sex sets, the male is 150 grams and 95 grams heavier, on the average, while the difference between the like-sexed pairs is almost the same, 39 grams, and 35 grams respectively for the male pairs and the female pairs.

Naeye (3) states, "Most twin measurements match the mean values for singletons through the 24th week of gestation. The subsequent growth of organs and the body are not as rapid. The dizygotic twins are larger than the monozygotic. This growth retardation has disappeared at the end of the first year of life." This is probably the explanation for the smaller weight of the like-sexed pairs, because of the increased incidence of monozygosity in such pairs.

Effect of sex on fetuses

The zygosity of the 6,356 pairs of known sex was not determined by placental relations, blood studies, or cytology. Therefore, we applied Weinberg's (1) differential method to separate statistically one-egg (monozygotic) and two-egg (dizygotic) pairs. This consists of substracting the total number of unlike-sex pairs (1,980) from the total number of like-sexed pairs (4,376). The number of remaining pairs (2,396) is the one-egg proportion of the sample (37.7 percent). This is based on the premise that in any large twin population there are an equal number of two egg male/male plus two egg female/female pairs as there are male/female plus female/male pairs, the two latter being from two eggs. This present estimated frequency of 37.7 percent for one egg pairs is slightly greater than reported in 1958, probably because of the larger sample and a change in the population making up the study.

When the weights of both infants are combined, the average weight of male/male pairs was 4,495 grams, of female/female pairs 4,463 grams, and pairs of mixed sex 4,619 grams. The fact that the average weight of the mixed sex pairs is 125 grams or more greater indicates that zygosity is a more important factor in affecting birthweight than sex. The small difference between the male/male weight of 4,495 and the female/female weight of 4,463 grams (32 grams), suggests the much lesser influence of sex as opposed to dizygosity.

Presentation of Twin Gestations

The presentation of 5,946 pairs of twins is summarized in Table IV. The presentations of like- and mixed-sex pairs do not differ statistically from one another. Therefore, it is concluded that neither sex nor zygosity appear to influence the presentation combination of twins.

Perinatal loss

One of the most compelling findings in any twin study is the perinatal mortality. Table V is a reflection of the observations of others. It is seen that the Obstetrical Statistical Cooperative Hospitals have experienced a small overall improvement since 1956—7 percent. The neonatal mortality, however, has improved by almost 21%, while the fetal mortality has worsened by almost 30%. This is, of course, adversely affected by the 219 deaths under 500 grams birthweight. When these abortions are subtracted, the fetal death rate is 3.14% and the neonatal mortality is 7.75%. Most obstetricians are interested in birthweight of 1000 grams and over for calculation of perinatal mortality. This allows comparison with studies by others, and raises little concern that some births and/or deaths have been omitted. This calculation reveals a fetal death rate of 2.09% and a neonatal mortality of 4.07%. This total perinatal mortality, 1000 grams birthweight and over, of 6.16% is to be compared with a singleton rate of 2% or less in many of the cooperative institutions. Table VI displays the mortality rates by birthweight for twins and singletons.

Contributions to perinatal mortality are summarized in Table VII. It is noteworthy that the difference in perinatal mortality between twin No. 1 and twin No. 2 is not the result of deaths during labor. In all weight categories, these rates are the same for twin No. 1 and twin No. 2. The excess perinatal loss for twin No. 2 results both from deaths before labor and neonatal mortality, but the contribution of neonatal mortality is more marked. In the

TABLE IV

Presentation

	V/V	V/B	B/B	V/T	B/T	Total
	%	%	%	%	%	
Male/Male	42.3	41.2	9.1	5.5	1.9	2,023
Female/Female	39.5	43.6	9.4	5.5	2.0	2,073
Male/Female	37.0	43.6	11.2	5.1	3.1	971
Female/Male	36.2	43.8	11.4	5.6	3.1	879
Total Percent	39.5	42.8	9.9	5.5	2.3	
Total Number	2,351	2,546	588	324	137	5,946

V = Vertex; B = Breech; T = Transverse Lie.

Spontaneous abortions and pairs in which both presentations not known—eliminated.

TABLE V

Literature Review

Author*	Years of Analysis	No. of Twins	Death Rate		Perinatal Loss	
			Fetal	Neonatal	Twins	Singletons
Kurtz (4)	1947–53	1,000	28	70	98	?
Bender (5)	1946-50	944	40	70	110	?
Donnelly (6)	1953–54	2,798	32	86	118	27
Guttmacher (7)	1896–1938	1,046	46	87	113	35
Potter (8)	1941–47	502	58	82	140	25
Stone (9)	?	384	26	115	141	?
Anderson (10)	1948–52	360	39	111	150	?
Tow (11)	1947–56	816	63	60	123	?
MacDonald (12)	1953–58	1,000	66	59	125	83
Spurway (13)	1946–58	706	60	62	122	?
Brown (14)	1950–60	626	58	38	96	34
Robertson (16)	1956–62	900	43	93	136	?
Farrell (17)	1957–63	2,000	?	?	161	?
Ferguson (18)	1955–58	3,218	37	56	93	22
Guttmacher & Kohl (1)	1950–56	2,654	37	96	133	35
Present Study	1961–72	12,788	48	76	124	45

* Numbers in parentheses are references.

TABLE VI

Perinatal Loss by Birth Weight
(Percent)

Birth Weight Grams	Twin No. 1		Twin No. 2		Total		Singletons 1972
	1958	1972	1958	1972	1958	1972	
Under 500	100.0	100.0	100.0	100.0	100.0	100.0	100.0
500–999	81.1	92.8	98.7	95.5	89.7	94.2	95.0
1,000–1,499	30.9	30.8	52.0	46.6	44.7	38.7	52.7
1,500–1,999	9.2	5.9	16.6	11.6	13.1	8.9	19.2
2,000–2,499	4.5	2.2	3.9	3.3	4.2	2.7	5.1
2,500–2,999	1.9	1.3	1.5	1.8	1.7	1.6	1.3
3,000–3,499	0.7	0.9	0.8	1.0	0.7	0.9	0.7
3,500+	0.0	0.8	0.0	2.0	0.0	1.4	0.9
Unknown	66.7	13.9	100.0	12.9	84.6	13.4	99.7
Total	11.7	10.8	14.9	13.9	13.3	12.4	4.9

total figures, the neonatal rate for twin No. 2 is 37% higher than for twin No. 1, while the fetal mortality before labor is only 19% greater. In the over-500 gram calculations, the neonatal difference is the same 37% excess, but the fetal death before labor contribution has increased to 32%. In the category of over 1000 grams, there is an 81% excess for neonatal and only a 37% excess for the fetal contribution. One may quibble about the method of calculation of these excesses for the second twin. However, it seems clear that the main reason for second twin perinatal mortality being 50% greater in the 1000 gram and over birthweight category is neonatal loss. The obstetrician must do all he can to reduce this excess mortality. One of the very important things he can do is see to it that there is not undue delay of the delivery of the second twin. Almost without exception, all reports in the literature (13, 15, 17, 19-23) call for delivery of the second twin within 15-20 minutes of the first delivery. MacDonald (12) calls to our attention that the second twin is slower to breathe and that the hazards in labor, except for cord prolapse, are much greater for the second twin. Breech presentation (19% in No. 1 and 42% in No. 2), breech extraction (13% in No. 1 and 32% in No. 2), compound presentation (.5% in No. 1 and 12% in No. 2), transverse lie (0.5% in No. 1 and 7% in No. 2), and a few more (26) cesarean sections for No. 2 infants than for No. 1 all contribute to this greater mortality. Thus the need for more instrumentation and more anesthesia is added to reduced placental circulation and increased probability of premature placental separation. There is no doubt that the increased perinatal mortality for twin No. 2 may be reduced by skillful obstetrical management (12, 14, 20, 24).

The excess mortality of the male is less easily explained. When the first twin is a male, its perinatal mortality is 10.4% while that of a No. 1 female is but 8.4%. When the perinatal mortality of the second twin is investigated, it is found that the male loss rate is 14.9% while the female rate is 10.4%, i.e., 30% less. Overall the loss rate is 9.4% for No. 1 and 12.6% for No. 2. The differences shown in Table VIII are significant at the 99% level of confidence. The

TABLE VII

Perinatal Mortality
1961-72

Birth Weight (Grams)	Twin No. 1				Twin No. 2				Total			
	DBL	DDL	NEO	TOT	DBL	DDL	NEO	TOT	DBL	DDL	NEO	TOT
Total	3.89	.52	6.43	10.84	4.63	.51	8.81	13.95	4.26	.52	7.62	12.40
Over 500	2.25	.53	6.54	9.32	2.98	.52	8.96	12.46	2.62	.52	7.75	10.89
Over 1,000	1.47	.35	2.90	4.72	2.02	.35	5.25	7.62	1.74	.35	4.07	6.16
1950-56												
Total	3.32	.98	7.39	11.69	3.99	.98	9.87	14.84	3.65	.98	8.63	13.26
Over 500	3.10	.98	7.40	11.48	3.34	.99	9.94	14.27	3.22	.98	8.67	12.87
Over 1,000	1.92	.80	4.09	6.81	2.49	.80	6.10	9.39	2.21	.80	5.09	8.10

DBL: Deaths before labor; DDL: Deaths during labor; NEO: Neonatal mortality; TOT: Total.

TABLE VIII

Perinatal Mortality by Sex and Birth Order

	Male		Female		Both	
	No. 1	No. 2	No. 1	No. 2	No. 1	No. 2
Percent Loss	10.4	14.9	8.4	10.4	9.4	12.6

	Twin No. 1		Twin No. 2		Both	
	Male	Female	Male	Female	Male	Female
Percent Loss	10.4	8.4	14.9	10.4	12.6	9.4

sequence of increasing perinatal mortality is Female A, Female B, Male A, Male B for vertex presentations. For transverse lies the No. 2 twins (female, then male) do better than the No. 1 babies (male better than female).

The male perinatal mortality is 1.24 times greater for the first twin, 1.43 times greater for the second twin, and 1.34 greater overall.

The perinatal mortality also varies by sex combinations. Table IX illustrates this. One must conclude that the ideal twin to be is No. 1 in the female/male variety. The next most favorable spot is to be No. 1 in the male/female combination. The male/male combination is the least desirable unless one is of unknown sex and then the system holds true for the No. 2 unknown. Because of the large number of infants involved in this compilation, almost all the observed differences are statistically meaningful.

The presentation of the babies for first and second delivered are shown in Table X. It is the usual display. There are more vertex presentations for No. 1 than for No. 2; there are many more breech presentaions for No. 2, as well as more transverse, face and compound presentations. The foregoing is true regardless of sex. Therefore, the lower perinatal mortality for No. 1 could be

TABLE IX

Perinatal Mortality by Sex-Pairs
(percent)

	Male/Male		Female/Female		Male/Female		Female/Male		Unknown		Total	
Discharged alive	87.6	83.5	90.9	88.9	91.4	89.5	91.3	86.0	12.2	6.8	88.2	84.9
Perinatal loss	12.4	16.5	9.1	11.1	8.6	10.5	8.7	14.0	87.8	93.2	11.8	15.1
Antepartum	2.8	4.1	2.2	2.7	1.5	1.8	1.7	2.2	3.4	0.7	2.2	2.9
Intrapartum	0.6	0.5	0.6	0.5	0.3	0.4	0.3	0.6	0.0	0.0	0.5	0.5
Neonatal	8.0	10.9	5.8	7.4	5.9	7.2	5.4	10.0	2.0	3.4	6.4	8.9
Abortions	1.0	1.0	0.5	0.5	0.9	1.1	1.3	1.2	82.4	89.1	2.7	2.8
Total over 500 grams	11.5	15.7	8.6	10.7	7.8	9.5	7.6	13.0	30.8	37.5	9.4	12.6
Difference Significant?	Yes		Yes		Borderline		Yes		No		Yes	
Total infants	2,179	2,179	2,197	2,197	1,032	1,032	948	948	147	147	6,503	6,503

TABLE X

*Perinatal Mortality by Presentation**
(percent)

Presentation	Twin No. 1				Twin No. 2				Both			
	M	P.M.	F.	P.M.	M.	P.M.	F.	P.M.	M.	P.M.	F.	P.M.
	%	%	%	%	%	%	%	%	%	%	%	%
Vertex	78.1	8.7	75.1	6.8	46.6	10.0	46.6	7.6	62.6	9.2	60.8	7.1
Breech	18.6	14.2	21.8	11.4	42.1	18.9	42.7	12.3	30.2	17.5	32.3	12.0
Face	0.4	41.7	0.5	0.0	0.5	21.4	0.4	15.4	0.4	30.8	0.4	7.1
Brow	0.3	0.0	0.3	12.5	0.2	0.0	0.2	14.3	0.2	0.0	0.2	13.3
Compound	0.6	44.4	0.4	50.0	2.1	23.4	2.0	15.9	1.3	28.0	1.2	21.3
Transverse	0.4	21.4	0.6	52.6	7.4	17.4	7.0	11.9	3.9	17.6	3.9	15.1
Unknown	1.6	28.0	1.3	22.0	1.3	33.3	1.1	30.6	1.4	30.3	1.2	26.0
Total	100.0	10.4	100.0	8.4	100.0	14.9	100.0	10.4	100.0	12.6	100.0	9.4
Numbers	3194	332	3136	264	3103	463	3215	334	6297	795	6351	598

* Spontaneous abortions eliminated

anticipated regardless of unfavorable placental dynamics. For almost all presentations, the perinatal morality is greater for males.

Method of delivery

Methods of delivery employed in this study differ very slightly from those reported by others except as they reflect the practices of the institutions involved and their obstetric philiosophies. It is interesting to note that twenty-six No. 2 twins were delivered by cesarean section after the No. 1 twin was delivered vaginally. Ten of these sections were performed because of a transverse lie. Only seven of the babies were discharged alive. Three operations were performed for premature separation of the placenta and three for fetal distress. All six of these babies were discharged alive. Three were done for prolapsed cord, with two survivors. Two were done for multiple pregnancy (sic)—both babies did well. Two were done for uterine dysfunction, with the loss of one baby. One section and one for breech produced two survivors and one for abnormality of the fetus resulted in a perinatal death. In summation then, these twenty-six cesarean sections salvaged 20 babies (77 percent). Three infants died prior to labor, two died during labor, and one died in the first twenty-four hours of life. This loss rate of 23 percent is large. The differing methods of delivery for twins No. 1 and No. 2 reflect the variance of presentations (Table X). The overview of methods of delivery is shown in Table XI. There is considerable variation of procedures according to the

TABLE XI

*Method of Delivery and Perinatal Mortality by Sex and Order**

Method of Delivery	Twin No. 1				Twin No. 2				Both			
	M.	P.M.	F.	P.M.	M.	P.M.	F.	P.M.	M.	P.M.	F.	P.M.
	%	%	%	%	%	%	%	%	%	%	%	%
Spont. vertex	49.0	12.3	48.7	9.6	29.2	15.4	30.0	11.2	39.3	13.4	39.2	10.2
Elect. forceps	19.7	4.0	19.5	2.5	9.0	4.6	8.6	3.3	14.4	4.3	13.9	2.7
Indicated forceps	4.1	4.6	2.9	5.4	2.8	5.7	2.5	5.0	3.5	5.1	2.7	5.2
Spont. breech	3.0	27.4	3.4	17.6	4.1	42.1	3.5	22.5	3.5	35.7	3.4	20.1
Oper. breech	12.3	13.2	14.4	10.4	30.7	17.7	32.2	11.4	21.4	16.4	32.4	11.1
Cesarean section	9.3	7.7	8.7	8.1	9.5	9.2	9.3	7.7	9.4	8.5	9.0	7.9
Vers. & extract.	0.1	0.0	0.3	70.0	12.4	15.0	11.7	10.6	6.2	14.9	6.1	12.2
Manual rotation	1.3	2.5	1.1	3.0	0.9	0.0	0.7	12.5	1.1	1.4	0.9	7.0
High forceps	—	—	0.0	100.0	—	—	0.2	0.0	0.0	0.0	0.1	16.7
Vac. extractor	0.9	13.8	0.7	0.0	0.5	0.0	0.8	12.0	0.7	8.7	0.8	6.3
Unknown	0.4	23.1	0.3	0.0	0.9	0.0	0.6	5.0	0.6	7.5	0.8	3.4
Total %	100.1	10.4	100.0	8.4	100.0	14.9	100.1	10.4	100.1	12.6	100.3	9.4
Total no.	3,194	332	3,136	264	3103	463	3,215	334	6,297	795	6,351	598

* Spontaneous abortions eliminated

birthweight. The detailed methods of delivery are shown in Table XII by birthweight of 1,500-1,999, 2,000-2,499 and 2500 grams and over. The prominence of certain procedures are lost unless they are inspected in relation to birthweight. For example, while cesarean section has an incidence of 9 percent to 10 percent in the entire study, in the weight group over 2500 grams, this incidence is 30 percent higher, about 12 percent. On the other hand certain methods are quite constant in frequency across the weight categories.

If the twin fetuses are alive prior to the onset of labor the outcome for twin No. 1 compares favorably with that for singletons. However, No. 2 suffers about double this risk of perinatal mortality. Twenty-four percent of the perinatal mortality suffered by No. 1 twins was due to death during labor, and 76 percent to neonatal deaths. For the No. 2 twins this relationship was 11 percent and 89 percent.

Only one-third of second twins are delivered spontaneously by vertex or breech, and one-half of first twins are so delivered. This further emphasizes the need for competent obstetric management. Well over half (56 percent) of second twins were delivered by cesarean section, version and extraction, breech extraction or decomposition, indicated low or midforceps, high forceps, or vacuum extractor.

The methods of delivery may be analyzed by birthweight and order of birth (Table XII). All sets of twins in which one or both infants died before labor have been excluded, so as not to confuse the influence of method of delivery upon perinatal mortality. The inherent risk of perinatal mortality below 1500 grams birthweight, at least 40 percent, makes evaluation of the method of delivery very confusing. Therefore, Table XII is restricted as noted above.

In the smallest weight group (Table XII) the loss of the second twin is 2.52

TABLE XIIA

*Method of Delivery by Weight and Birth Order**

Infant Weight 1,500–1,999 Grams

Method of Delivery	No.	First Twin		% Loss	No.	Second Twin		% Loss
		I.P. Deaths	NEO. Deaths			I.P. Deaths	NEO. Deaths	
Spontaneous vertex	476	0	15	3.2	296	1	28	9.8
Elective forceps	175	1	5	3.4	87	0	6	6.9
Indicated forceps	32	0	3	9.4	22	0	1	4.5
Spontaneous breech	32	1	2	9.4	52	0	2	3.8
Operative breech	150	1	2	2.0	376	0	34	9.0
Cesarean section	60	2	2	6.7	70	2	4	8.6
Version & extraction	2	0	0	0.0	138	0	18	13.0
Manual rotation	8	0	0	0.0	7	0	2	28.6
High forceps	0	0	0	0.0	2	0	0	0.0
Vacuum extractor	5	0	1	20.0	3	0	1	33.3
Unknown	1	0	0	0.0	4	0	0	0.0
Total	941	5	30		1,057	3	96	
Percent		0.53	3.19	3.72		0.28	9.08	9.36

* Sets in which one or both infants died before labor excluded

TABLE XII B

*Method of Delivery by Weight and Birth Order**
Infant Weight 2,000–2,499 Grams

Method of Delivery	No.	First Twin		% Loss	No.	Second Twin		% Loss
		I.P. Deaths	NEO. Deaths			Deaths	Deaths	
Spontaneous vertex	942	0	5	0.5	604	2	5	1 2
Elective forceps	445	0	4	0.9	187	0	1	0.5
Indicated forceps	71	0	1	1.4	44	1	0	2.3
Spontaneous breech	50	1	0	2.0	49	0	1	2.0
Operative breech	244	0	4	1.6	622	3	11	2.3
Cesarean section	156	4	2	3.8	186	2	6	4.3
Version & extraction	2	0	0	0.0	235	0	0	0.0
Manual rotation	25	0	0	0.0	14	0	1	7.1
High forceps	0	—	—	—	1	0	0	0.0
Vacuum extractor	13	0	0	0.0	9	0	0	0.0
Unknown	5	0	0	0.0	18	0	0	0.0
Total	1,935	5	16		1,969	8	25	
Percent		0.26	0.82	1.08		0.41	1.27	1.68

* Sets in which one or both infants died before labor excluded

TABLE XII C

Method of Delivery by Weight and Birth Order
Infant Weight Over 2,500 Grams

Method of Delivery	No.	First Twin		% Loss	No.	Second Twin		% Loss
		I.P. Deaths	NEO. Deaths			I.P. Deaths	NEO. Deaths	
Spontaneous vertex	1,128	2	3	0.4	681	1	6	1.0
Elective forceps	515	0	0	0.0	256	0	1	0.4
Indicated forceps	93	0	0	0.0	85	0	1	1.2
Spontaneous breech	56	0	0	0.0	40	0	0	0.0
Operative breech	306	2	1	1.0	643	3	2	0.8
Cesarean section	295	1	1	0.7	273	1	0	0.4
Version & extraction	0	—	—	—	280	0	3	1.1
Manual rotation	37	0	0	0.0	31	0	0	0.0
High forceps	1	1	0	100.0	2	0	0	0.0
Vacuum extractor	29	0	0	0.0	28	0	1	3.6
Unknown	10	0	0	0.0	11	0	0	0.0
Total	2,470	6	5		2,340	5	14	
Percent		0.24	0.20	0.44		0.21	0.60	0.81

* Sets in which one or both infants died before labor excluded

times the loss of the first twin. This relationship is retained in the heavier infants—1.55 for 2,000-2,499 grams and 1.84 for the group of 2,500 grams and over. Spontaneous deliveries occur with a frequency of 54 percent in the No. 1 babies of small size, 51 percent in the middle group and 48 percent in the term sized infants. For the No. 2 babies 33 percent were delivered spontaneously in the small group. The necessity for operative termination for the second baby is rather consistent across birthweight categories.

Cesarean section frequencies are shown in Table XII and are summarized here:

	No. 1	No. 2
1,500–1,999	6.4%	6.6%
2,000–2,499	8.0%	9.4%
2,500+	11.9%	11.7%

This reflects that which is observed in all deliveries; the incidence increases as the birthweight increases. The perinatal mortality is at or higher than the average rate for weight and order of birth. This is related to the fact that the indications are somewhat different for cesarean section in twin pregnancy. Sixty-eight percent of these operations were primary. The indications in order of frequency were (Table XIII): prolapsed cord, uterine dysfunction, antepartum hemorrhage, premature rupture of membranes, contracted pelvis, breech, toxemia, fetal distress, transverse lie, diabetes, elderly primigravida and intrapartum infection. These indications vary in frequency from 16.3 percent to 1.5 percent. There remain 17.1 percent of primary cesarean sections performed for a large variety of infrequent indications. In single pregnancies 50 percent or more of primary sections will be done for mechanical dystocia of one sort or another; here only 30 percent of the sections were performed for this group of indications. The perinatal mortality associated with the twin indications is higher.

Version and extraction of the second twin was done with equal frequency

TABLE XIII

Indications for Primary Cesarean Section

Indication	Percent of Total
Prolapse of Cord	16.3
Uterine Dysfunction	15.8
Antepartum Hemorrhage	10.9
Abnormal Presentation	10.9
Breech	6.6
Transverse	2.8
Other	1.5
Contracted Pelvis	7.1
Premature Rupture of Membranes	7.1
Toxemia	6.4
Fetal Distress	4.3
Diabetes	2.3
Elderly Primigravida	1.5
Intrapartum Fever	1.5
Others	15.9
Primary Sections	392
Repeat Sections	177
Total Sections	569

across all weight groupings. The perinatal mortality exceeded the expected to an appreciable degree only in the smallest weight category. In the others, it was within the expected statistical range of the average perinatal mortality rate.

Version and extraction of the second twin was the method of delivery 12 per cent of the time. This was less frequent than we had anticipated. Undoubtedly some of the operative breech deliveries of the second twin actually were version and extractions. For procedures done more than 1 percent of the time, these two procedures carry the highest perinatal mortalities. They are almost always higher than the average for a specific group or for all deliveries of second twins over 1,500 grams. Therefore, the desirability of *external* version of the second twin, converting it to a vertex, is apparent; and the procedure should be attempted.

Elective forceps operations occurred with about equal frequencies in all the weight groups by order of birth. At all times, the perinatal mortality associated with this operation was less than the average for the specific grouping.

Malformations

Table XIV shows the relative frequency of major and minor malformations for twin and single gestations. The comparisons of incidence of congenital malformations among studies is very difficult. There is wide variation in the interpretation of the terms and in the diagnostic procedures employed. In 1956, Book and Fraccaro (25) showed that the incidence of malformations varied from 0.55 percent when reported by a group of obstetricians to 7.54 percent when reported by a group of pediatricians on samples from the same community. There appears to be no significant difference between first and second twins, but an appreciable difference between twins and singletons, 6.25 percent versus 3.50 percent.

In this study the major malformations include the central nervous system, the cardiovascular system, the gastrointestinal systems, and the mouth or palate. The category minor malformations, includes all abnormalities of the extremities and others not listed above.

It appears from this study and others that the frequency of congenital malformations is one and one half to two times greater in twins than in singletons. This may be due to the presence of an estimated 38 percent

TABLE XIV

Incidence of Congenital Malformations

	Singletons		Twins	
	No.	%	No.	%
Major malformation	655	1.05	267	2.12
Minor malformation	1,529	2.45	520	4.13
Total infants	2,184	3.50	787	6.25

monozygosity. Malformations occurring in monozygous twins would automatically increase the frequency for all twins. This is especially so if the assumption is correct that malformations are more common in monozygotic than in dizygotic twins. Unfortunately, documentation of this assumption is poor.

Weight differences

For 6,418 sets of twins, there was information as to the birth weights of both infants in the set. The individual weights were plotted against each other in 100 gram increments. It was then possible to produce Table XV, which reflects the differences between twins in the various sets. In almost 18 percent of sets, the two babies weighed within 100 grams of one another. When there was a difference of greater than 100 grams, it was more likely that the first baby was heavier than the second baby. In 79 percent of the sets the two babies were within 500 grams of one another at birth. Another 18 percent were within 500 and 999 grams of one another at birth. Table XV displays the probability associated with differences in birth weights for sets of twins. Forty-three

TABLE XV

Difference in Birth Weight

Grams	A > B	A < B	Total
Less than 100	—	—	17.8
100-199	10.8	11.4	22.2
200–299	8.7	9.0	17.7
300–399	6.5	5.5	12.0
400–499	4.9	4.5	9.4
500–599	3.6	3.0	6.6
600–699	2.8	2.0	4.8
700–799	1.6	1.4	3.0
800–899	1.1	1.0	2.1
900–999	1.0	0.5	1.5
1,000–1,099	0.7	0.3	1.0
1,100–1,199	0.3	0.1	0.4
1,200–1,299	0.2	0.1	0.3
1,300–1,399	0.1	0.2	0.3
1,400–1,499	0.2	0.1	0.3
1,500–1,599	0.1	0.03	0.13
1,600–1,699	0.1	0.02	0.12
1,700–1,799	0.1	—	0.1
1,800–1,899	0.1	0.03	0.13
1,900–1,999	0.03	0.03	0.06
2,000–2,099	0.1	—	0.1
2,100–2,199	0.02	—	0.02
2,200–2,299	0.02	—	0.02
2,300–2,399	0.03	—	0.03
2,700–2,799	0.03	0.02	0.05
3,000–3,099	0.03	—	0.03
Total	43.16	39.23	100.19

percent of the time, the first twin was heavier, 39 percent of the time the second was heavier, and 18 percent of the time they were within 100 grams of one another at birth. Larger differences in birth weight, 1,000 grams or more, are to be expected only in about 3 percent of twin sets. The greatest difference, 3,000 grams, was observed only twice.

Conclusion

There is little reason to change the conclusion drawn by us in 1958. It is still desirable to carry twin pregnancies to at least the 35th week of gestation, for by this time the perinatal mortality is below 5 percent. The chances of postponing the spontaneous onset of labor until this time may be enhanced by hospitalization and bed rest during the 28th–32nd weeks of pregnancy (11, 12, 15, 26).

Delivery of the first twin spontaneously or by elective forceps, if a cephalic presentation, is greatly desired. Deliver the second forthwith, "while the cervix is still fully dilated immediately after the first delivery, rupture the membranes and deliver the second twin from a potentially dangerous situation." When possible, conversion of the second twin to a cephalic presentation by combined intrauterine and extrauterine manipulation, while the membranes are intact, is a desirable procedure. Then rupture of the membranes and guiding of the head into the pelvis will make possible either spontaneous vertex delivery or an elective forceps operation.

Summary

The average birth weight of a twin was betwwen 2,231 grams and 2,336 grams depending upon the sex composition of the pair. The male/female pairing is the heaviest and the female/female pairing is the lightest. The median duration of the pregnancies was 36.7 to 37.0 weeks gestation. The birth weight of a twin is effected by duration of pregnancy, sex and zygosity. Males are heavier than females and two egg twins are heavier than one egg twins.

The median duration of pregnancy is very similar for the various twin pairs. It is 36.7 weeks for male/male, 37 weeks for female/female and male/female and 36.8 weeks for female/male sets.

On the average the twin fetus gains weight rapidly until the 38th week. After that the weight gain per week diminishes until it is negative after the 43rd week.

Perinatal loss is closely related to gestational age and birthweight. The perinatal loss for twins of a given birthweight is less than for singletons of the same birthweight, until 2500 grams is reached. Thereafter the reverse is true.

The total perinatal mortality for all twins is 12.4 percent. For those over 500 grams birthweight it is 10.9 percent and for those over 1,000 grams birthweight the perinatal loss is 6.16 percent (approximately 3 times that for singletons). In our 1950–1956 series the perinatal loss was 8.1 percent for the twins over 1,000 grams birthweight. The current report reflects an improvement of 25 percent.

Forty percent of twins present as both vertex. Forty-three percent of the

time one is a vertex and one is a breech. Ten percent of the time there are two breeches and a transverse is combined with a vertex or breech in the remainder, (7.0 percent).

Vertex presentation is associated with the best salvage for both infants.

Unlike sexed pairs enjoy a better salvage rate than do like sexed pairs; no doubt related to dizygosity.

In all weight categories, regardless of birth order, salvage is greatest for vertex presentations delivered spontaneously or by elective forceps. Twins delivered by version and extraction have an appreciable mortality in the 1,500–1,999 and over 2,500 gram weight categories. The loss rates are above the average for the weight category. Cesarean section, at a frequency of 4.6 percent delivered 9.2 percent of the babies. The average cesarean section rate for the Cooperative during this period was 6.4 percent. The indications for cesarean section in twins are prolapsed cord, dysfunctional labor, toxemia, antepartum hemmorhage, and abnormal presentation of first infant, in that order.

The greater loss of second infants is due to increased neonatal deaths rather than fetal deaths before or during labor.

Congenital malformations are 1.78 times more frequent in twins than in singletons.

The weight differences between these infants of the same gestation show that 79.1 percent are within 500 grams of one another at birth. Another 18.0 percent are between 500 and 999 grams. Thus in 97.1 percent of twin births the two twins exhibit at birthweight difference of less than 1,000 grams.

There were 26 second babies delivered by cesarean section whose first twin was delivered vaginally. The procedure does not insure a survivor. Twenty-three percent of these second twins were not salvaged.

The maternal mortality rate is high when compared to that for singleton births. In this study there were seven deaths including abortions for a rate of 10.8 per 10,000 patients. The comparable rate for singletons is 4.1 per 10,000 births.

The incidence of pregnancy toxemia is 13.3 percent. This frequency is over twice that seen in single pregnancies in the Cooperative in the same time period.

Acknowledgment

The sets of twins have been contributed by 32 different hospitals in the Obstetrical Statistical Cooperative. The dates indicate the periods of time for which data were used:

Baltimore City Hospital	1967-1968
Brookdale Hospital	1961-1965
Brooklyn-Cumberland Medical Center	1965–1972
University of California (S. F.)	1961-1972
University of Colorado Hospital	1961–1966
Coney Island Hospital	1962–1972
Elmhurst City Hospital	1966-1968
University of Florida Hospital	1972
Good Samaritan Hospital	1968 1969
Greenpoint Hospital	1964-1972
Harlem Hospital	1963–1970

Hartford Hospital	1961–1974
Jewish Hospital of Brooklyn	1962–1972
Kings County Hospital	1961–1972
Long Island College Hospital	1964–1972
Long Island Jewish Hospital	1961–1971
Lutheran Hospital-Baltimore	1966–1969
Maimonides Hospital	1961–1972
University of Maryland Hospital	1961–1967
City of Memphis Hospital	1966
Metropolitan Hospital	1961–1968
Nassau County Medical Center	1969–1972
University of Oklahoma	1962–1969
Philadelphia Lying-In Hospital	1961–1964
Queens General Hospital	1965–1968
Royal Victoria Hospital	1961–1970
St. Lukes Hospital	1965–1972
San Francisco General Hospital	1961–1970
Sinai Hospital-Baltimore	1961–1965
State University Hospital-Brooklyn	1967–1972
University of Utah	1961–1969
Yale-New Haven Hospital	1961–1966

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Alcoholic Pancreatitis

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The purpose of this paper is to present recent works on the relationship between chronic alcoholism and pathology of the pancreas, particularly those results which have been obtained in our laboratory during the last year. Papers already analyzed in previous reviews (1, 2) either will be summarized or omitted.

1. *During the course of alcoholic pancreatitis, the first lesion visible at the optical level is the formation in the pancreatic ducts of protein precipitates or plugs which obstruct the ducts and later calcify, forming stones.*

This assertion is founded on pathological studies in man and experimental animals.

A. A three-dimensional reconstruction of the pancreatic ducts has been made from the secondary branches of the main duct to the terminary acini in large surgical specimens of the pancreas from patients with alcoholic calcifying chronic pancreatitis, chronic pancreatitis secondary to the obstruction of the main pancreatic duct by slowly growing carcinomas, and in normal pancreases (3) (Fig. 1). Serial sections of the fragments of pancreas, 7.5-12.5 Mμ in thickness, were made. The average number of sections for each duct was 800. After staining, a paper tracing was made of each section by means of a projecting microscope. The plane of reconstruction could be chosen to give the best perspective of the canal. The tracings were superimposed at intervals to make a model of the duct. The pathway of the ducts was then drawn from the model on a plane parallel to its axis. In alcoholic chronic calcifying pancreatitis, protein plugs may not be present in an individual section, but are always found in three-dimensional reconstructions. These plugs are typically concentric laminar concentrations of protein. Many of them are calcified. Calcification begins at the periphery, but every possible transitional form of protein precipitate may be present. At one extreme, there are the mature protein plugs, typically concentric laminar concentrations of protein, often calcified; at the other end of the spectrum, there are the delicate films of protein which may be deposited by the pancreatic juice in entirely normal ducts. The fact that only one out of five plugs in the specimens stained with periodic acid-Schiff indicated that mucopolysaccharide usually cannot be found in such specimens. The duct epithelium in contact with a plug or

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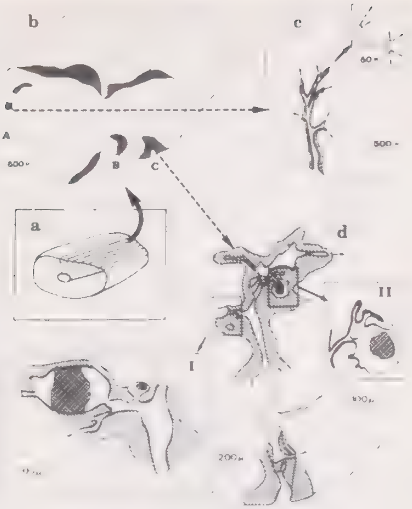

FIG. 1. Three-dimensional reconstruction of pancreatic duct system constructed from specimens obtained from resections in patients with alcoholic pancreatitis.

calculus usually shows evidence of damage. But it is important to point out that occasionally, protein plugs may be found in entirely normal ducts, draining normal lobules.

The irregularity of the distribution of the lesions is typical of chronic calcifying pancreatitis (CCP): one duct and the acini which it drains being normal in every respect, side by side with ducts and lobules with advanced lesions.

On the contrary, in pancreatitis secondary to an obstruction in the main pancreatic duct, the alterations in the ducts are much less striking. The lumen is empty and only very rarely are any protein plugs detectable.

Thus, while the precipitation of protein in the duct is rarely observed in pancreatitis secondary to an obstruction, it is a regular feature of alcoholic chronic calcifying pancreatitis where it can be found in segments of the gland which are normal at the optical level in every respect. It is, therefore, reasonable to assume that these protein precipitates from which pancreatic stones originate, are also the cause of the other pancreatic lesions by obstructing the ducts.

B. A multivariate analysis of the histologic characteristics of cases of chronic pancreatitis has been done (4) (Fig. 2). The tissue sections were examined on two occasions by two pathologists, neither of whom knew the patients or the diagnosis. When discordance was found between interpretations, the sections were studied by a third pathologist. Fifty-four different parameters were investigated. It appears that in chronic alcoholic pancreatitis, one of the most characteristic features is the presence of protein plugs in the ducts.

C. Setting aside a few isolated, poorly investigated cases, animal pancreatic lithiasis has principally been observed in bovines (5). It was described by

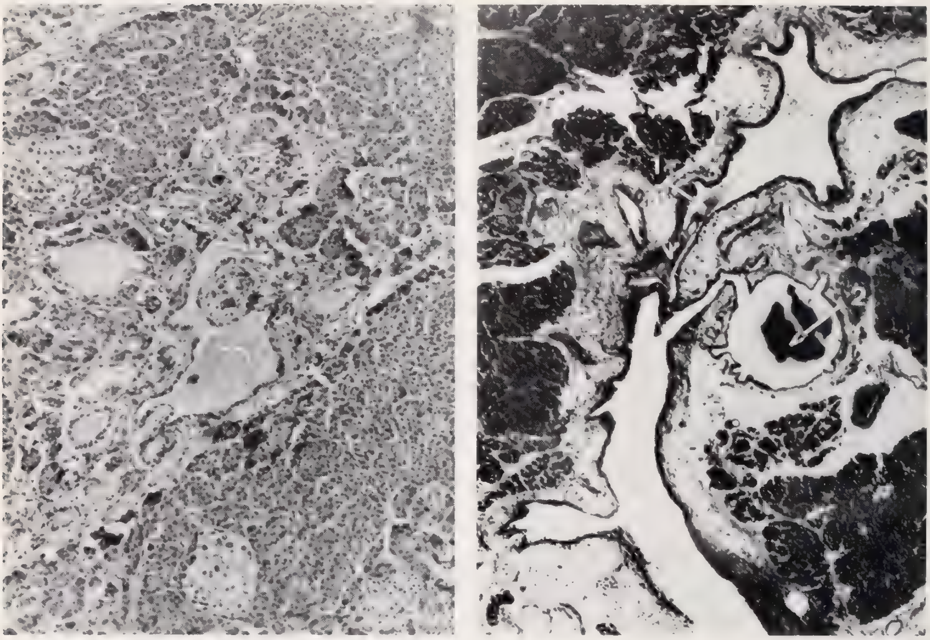

FIG. 2. Sections of human pancreas showing characteristic proteinaceous plugs in ducts.

Wallaston (quoted by Pemberton) (6), and has been the subject of recent reviews (7–9). The calculi are present in the pancreatic ducts, primarily the main duct. While their structure is the same as that of the calculi found in the human subject, the lesions to which they give rise are very different, for they are essentially centered on the main duct and disappear toward the periphery of the gland which is normal.

Lesions very similar to chronic calcifying pancreatitis have recently been observed in the rat (10–12). These lesions are, in fact, localized in foci with a lobular distribution, initially surrounded by normal parenchyma. A decrease in the number of acini is noted in these foci, as well as the development of rounded cavities surrounded by cubical epithelium and containing protein plugs very much like those found in man, some of them being calcified into actual stones. In some rare instances, protein plugs may be found in normal ducts. The disease appears spontaneously in the rat, the likelihood of its occurrence perhaps increasing with age. Its frequency is considerably increased by chronic consumpton of alcohol. Thus, the rat presents a good model for studying alcoholic chronic calcifying pancreatitis of man. Identical lesions have also been seen in the rabbit.

In the juice of dogs habituated to daily consumpton of ethanol (2 g/Kg/day) for at least three months, the formation of protein precipitates rich in calcium and similar to recently formed pancreatic stones in man have been observed (13). One of these dogs has been recently autopsied. While no lesions of chronic pancreatitis were seen, some of the ducts were filled with protein plugs.

2. *What is the nature of the protein precipitates observed in the ducts of CCP patients?*

It has been shown above that mucoproteins were not an usual constituent of intraductal protein plugs. When, in the course of a surgical operation for alcoholic chronic pancreatitis, a catheter is placed in the duct of Wirsung, it is easy to collect pure pancreatic juice for some days. In this pathological juice, it is common to observe protein precipitates, the frequency of which is probably increased by alcohol consumption (1). After staining, these precipitates have the same histochemical characteristics as the protein plugs observed in the ducts. They have been, at least partially, redissolved at pH 9 in our laboratory. As judged by disc-electrophoresis and immunoelectrophoresis, these redissolved precipitates are similar to the proteins of the pancreatic juice.

Following is a comparison of the protein in the pancreatic juice of normal individuals with that of patients with chronic calcifying pancreatitis.

A. As in different animals, the greatest part of pancreatic juice proteins are represented by enzymes, coenzymes or enzyme inhibitors. These enzymes are present in the juice from normal controls, and from patients with CCP. Their relative proportion is probably not different between patients and controls.

B. Serum proteins (14, 15): The presence of serum proteins in the pancreatic juice has been studied in samples of patients without pancreatic diseases and with chronic calcifying pancreatitis. The pancreatic juice was collected by catheterization of the main pancreatic duct and was pure. The proteolytic enzymes were in the zymogen form. Immunochemical study showed that in normal juice, serum albumin represents 1.26 ± 0.36 per cent of total protein of pancreatic juice, IgG 0.23 ± 0.039 and IgA 0.18 ± 0.034. The albumin/IgG ratio is not significantly different from that in human serum while the albumin/IgA and IgG/IgA ratios differ significantly. This fact favors a local synthesis of IgA rather than a specific excretory mechanism. In pathologic juice, an increased level of serum protein has been found: 12.45 percent of the total protein compared to 1.8 percent in normal juice. Albumin comprises 8.16 percent of the total protein, IgG 2.84 percent, IgA 0.83 percent and IgM 0.91 percent. Transferrin and alpha-macroglobulin are present but were not estimated. The albumin/IgA and albumin/IgG ratios again favor the hypothesis of a local synthesis of this immunoglobulin as in normal juice. Therefore, serum proteins are present in normal pancreatic juice, but their concentration is significantly increased in pathologic juice. One possible explanation is the importance of ductal epithelium lesions in CCP. In effect, it has been shown (3) that the duct epithelium in contact with a plug of calculus usually shows evidence of damage (Fig. 3). Atrophic epithelium adjacent to the plugs tends to disappear entirely at a later stage. This certainly facilitates the penetration of interstitial fluid into the ducts. In this case, the increased concentration of blood proteins and especially albumin could not be the primary cause of intraluminal protein precipitation.

C. The cross adsorption of antisera against pancreatic juice showed the presence in the pathologic juice of a protein which was not detectable in

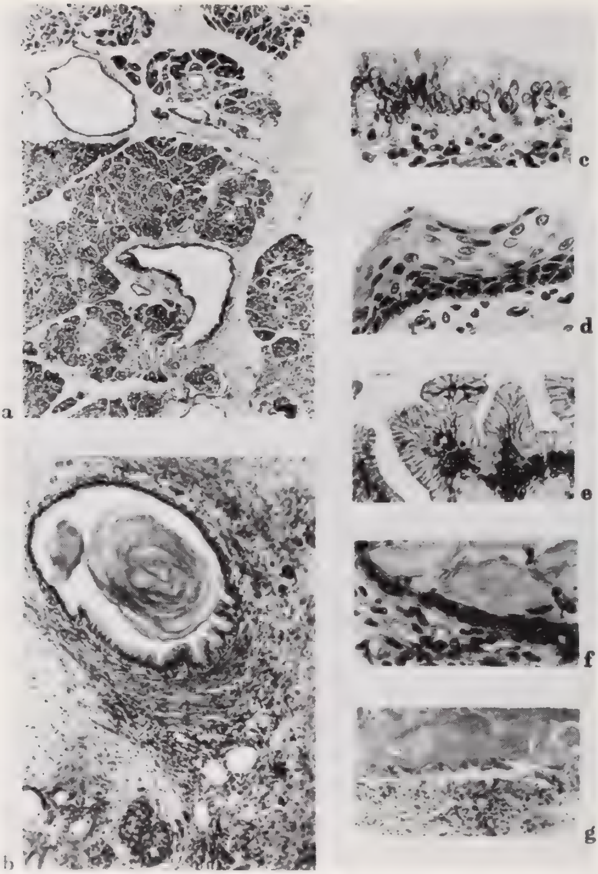

FIG. 3. Ductal epithelial changes in chronic calcific pancreatitis and their relationship to proteinaceous plugs.

controls (15). This additional protein is not degraded by the activated enzymes when present in pancreatic juice. By gel filtration on Sephadex G 100, polyacrylamide gel electrophoresis and immunoelectrophoresis, this protein has been shown to be lactoferrin (16). Lactoferrin is an iron-binding protein mainly secreted by the mammary glands and identified in various external secretions, e.g., saliva, bronchial mucus and tears (17), as well as in the specific granules of neutrophylic leucocytes (18). The level of lactoferrin in pancreatic juice of men with CCP is very low: 0.03 to 0.34 percent of total proteins.

Since lactoferrin has been found in neutrophylic leucocytes, it could postulate as contamination caused by leucocyte lysis in the pathological pancreas. However, when alkaline phosphatase was a marker of leucocytes and its activity assayed in pathologic pancreatic juices for this activity, no relation was found between phosphatase activity and lactoferrin presence. Most samples did not contain any phosphatase activity. Therefore, lactoferrin in pathologic pancreatic juice is probably not due to a leucocyte contamination, but is rather a component of pancreatic secretion. Masson and our laboratory found lactoferrin in normal serum in a very low concentration (1 μg/ml). Therefore, lactoferrin presence in pathologic pancreatic juice could be the result of an exaggerated passage of this protein from serum into the pancreatic juice. Indeed, the pancreatic origin of this protein has been shown by indirect immunofluorescence technic (19). Seven human pancreases were studied, three from patients with chronic calcifying pancreatitis, the four others from individuals without any pancreatic disease. In all cases, fluorescence has been found in the acinus lumen and in the cytoplasm of acinar cells, where it is more intense in the apical part of the cell. Pancreases from patients exhibit a more intense fluorescence than normal pancreas. The apparent contradiction between the presence of lactoferrin in normal pancreatic tissue by immunofluorescence, and its absence from normal pancreatic juice as judged by immunodiffusion techniques is explained by the different sensitivity of these two techniques. Thus, the detectable presence of lactoferrin in pancreatic juice by immunodiffusion is apparently characteristic of chronic calcifying pancreatitis. This could either be a consequence of the disease or play a part in its pathogenesis. Human lactoferrin associated strongly with acidic macromolecules to form complexes (20), a property possibly related to the phenomenon of protein precipitation observed in the pancreatic ducts of men with chronic calcifying pancreatitis. The fact that lactoferrin has been found in the pancreatic juice without any correlation between its concentration and the intensity of lesions favors the second hypothesis. In one patient with lesions in an early stage, lactoferrin was present in the pancreatic juice but the pancreatic function test was normal. This shows at least that the presence of lactoferrin in pathological pancreatic juice may be of clinical interest.

As endoscopic catheterization of the pancreatic duct is not always possible, it was necessary to develop a technique for the estimation of pancreatic lactoferrin in the duodenal juice (21). In normal subjects lactoferrin was found in saliva, but not in gastric juice nor in bile. Therefore, a technique for collecting the human duodenal juice with a rubber tube and preventing its contamination with saliva was devised. Duodenal juices so obtained are tested by double diffusion on 1.5 percent agarose plates by Ouchterlony technique. Lactoferrin is estimated before and during two periods of 15 minutes each after intravenous injection of 1 clinical unit of secretin and 3 Crick-Harper-Raper units CCK-PZ. The test was considered as positive when lactoferrin increased or was present only after CCK-PZ injection; inconclusive when it was present at similar concentration before and after; and negative when it was not present after CCK-PZ. The test was positive in the great majority of patients with chronic calcifying pancreatitis, while it was negative in 9 cases with acute pancreatitis or cancer of the pancreas. In controls without detectable pancreatic diseases, the test has been found to be positive approximately 10 percent of the time. The presence of lactoferrin at detectable concentrations at the very beginning of the disease, and its presence in a small proportion of the normal population could be explained by an inherited pattern of secretion, facilitating the action of alcoholism on the pancreas. The presence of lactoferrin in normal pancreatic tissue (indirect immunofluorescence) is not against this hypothesis. It is no longer necessary to consider that certain pathologic states must be characterized by the presence of a protein which is completely absent in normal subjects. Rather, it seems that the antigen is present in all normal subjects but that the concentration of this protein is at such a low level that the techniques used are not sensitive enough to detect these minute quantities. This has been demonstrated for alpha-fetoprotein and carcinoembryonic antigen.

D. Modifications of calcium concentration in the pancreatic juice could play a part in the precipitation of proteins. It is known that pancreatic lithiasis occurs in hyperparathyroidism (22). Indeed, the calcium concentration is increased in the pancreatic juice during the course of chronic calcifying pancreatitis (23, 24), but this is certainly not specific for this disorder since an increased concentration of calcium has been found in other types of pancreatic diseases including cancer and acute pancreatitis (25). Besides, in chronic alcoholic dogs it is possible to observe the formation of protein precipitates rich in calcium in the pancreatic juice when the calcium concentration of the juice is significantly lower than in normal controls (13). In fact, the formation of pancreatic stones in hyperparathyroidism can be explained without consideration of calcium concentration in the juice. Goebell et al (26) have shown that hypercalcemia induces an increased secretion of proteins by the pancreas, and Tiscornia et al (27) found that this hyperconcentration of proteins in the juice was followed by the precipitation of these proteins and the formation of pancreatic plugs. Thus, the protein plugs observed in chronic alcoholic pancreatitis as in any other type of chronic calcifying pancreatitis, are formed mainly by the normal, enzymatic proteins of the pancreatic juice. The role of the abnormal secretion of lactoferrin has been discussed. An increased secretion of calcium is very probably not the primary cause of the inflammation but it cour, in late stages, favor the calcification of the plugs and the formation of visible stones.

3. *Chronic consumption of alcohol favors the precipitation of proteins in the pancreatic juice and the formation of chronic calcifying pancreatitis.*

This concept is supported by experimental studies. On the rat drinking *ad libitum* 20 percent ethanol for at least two years, a very significant increase in the frequency of pathology comparable to the human chronic calcifying pancreatitis is observed (12). The excretion of pancreatic protein precipitates and stones in the pancreatic juice of chronic alcoholic dogs is further evidence (13). It has been found that in patients with chronic calcifying pancreatitis, the consumption of ethanol but also of proteins and fat, was significantly higher than in normal controls; data was derived from studies by Dani in Belo-Horizonte (Brazil), Mott in Sao Paulo (Brazil), and Goebell in Germany. An initial international survey on nutrition and pancreatitis (28), with the help of 24 centers in 16 countries in Africa, Latin America, Asia and Europe, disclosed a geographic distribution of chronic calcifying pancreatitis linked with alcoholism in countries with a high protein-high fat diet. There was also a high incidence of chronic pancreatitis in countries where there is protein deficiency malnutrition. A second nutritional survey done for the World Congress of Gastroenterology (Mexico, 1974) confirms and amplifies the conclusions of the first inquiry. Alcoholism and malnutrition are primary etiologic factors of chronic calcifying pancreatitis. The part played by alcoholism is particularly important in Europe but also significant in Latin America—and in India and Africa, two parts of the world where malnutrition in childhood is certainly responsible for the great majority of cases. All types of alcoholic beverages were encountered in the study, including wine, spirits, beer, apertifs, whiskey, sake, and cachaça. The consumption of fat, protein and also carbohydrates is significantly higher in patients with chronic alcoholic pancreatitis. The number of cigarettes smoked is also higher in the chronic calcifying pancreatitis, probably due to the fact that alcoholism and cigarette smoking are frequently associated. The shortest duration of alcohol consumption before the first attack of pancreatitis is two years.

Thus, chronic alcoholic and calcifying pancreatitis may occur in any race or climate whenever the consumption of ethanol, fat and protein is high.

Finally, chronic alcoholism plays a dominant role in the etiology of chronic pancreatitis. It is generally associated with an overconsumption of protein and fats but not with malnutrition, which is by itself a cause of similar lesions. In rats and dogs, chronic consumption of ethanol provokes the formation of protein precipitates in the pancreatic juice and ducts and, at least in rats, of chronic calcifying pancreatitis.

4. *The possible mechanisms for alcohol to provoke the formation of protein precipitates in the pancreatic ducts has been studied in the dog.*

A series of experiments was done in two groups of six dogs provided with pancreatic and gastric Thomas' cannulae, and fed with a standard diet enriched in protein and fat by giving a large supplement of meat. Three of these dogs had been previously submitted to a bilater vagotomy. Half of the dogs were given gastric cannula 2 g/Kg ethanol diluted to 15 percent each day for one to more than two years. The pancreatic secretion of these animals was sequentially studied with intravenous prolonged infusion of secretin, CCK-PZ, gastrin, atropine, pentolinium, and reserpine. The pertinent findings of these studies could be summarized:

a. The action of intravenous infusion of ethanol (1.5 g/Kg) on pancreatic secretion depends upon whether or not the animals are accustomed to the regular consumption of 2 g/Kg ethanol. In animals not accustomed to the regular consumption of ethanol, the intravenous infusion of ethanol provokes a strong inhibition of the pancreatic secretion. Secretion of protein is decreased more than secretion of water and bicarbonate. This finding has been confirmed in man repeatedly (29, 30). This inhibition is suppressed by intravenous infusion of 75 μg/Kg/h atropine or of 0.75 mg/Kg/h pentolinium, and partially abolished by vagotomy. However, previous reserpinization is ineffective. This means that in animals which are not adapted to alcohol consumption, alcohol excites a cholinergic inhibitory mechanism mediated through the vagus nerve and probably arising in the brain. On the other hand, in animals adapted to the regular daily consumption of 2 g/Kg ethanol, intravenous infusion of 75 μg/Kg/h atropine or of 0.75 mg/Kg/h pentolinium, marked for the secretion of proteins than for the secretion of water and bicarbonate. The transition between "nonalcoholic state" and alcoholism starts at about the sixth week of regular alcohol consumption and is complete at the end of one year.

B. In "chronic alcoholic dogs," the consumption of ethanol, fatty acids and proteins provokes a pancreatic secretion abnormally rich in protein but the basal secretion is not modified. This abnormal secretion of proteins appears to derive from the following mechanisms: 1) in the alcoholic dog the intravenous infusion of 0.7 to 1.5 g/Kg/h ethanol, instead of decreasing the pancreatic secretion of protein, increases protein secretion. This increase is suppressed by perfusion of atropine, but not by pentolinium, vagotomy or reserpinization. At this stage, therefore, alcohol acts through a cholinergic mechanism at the level of the intrapancreatic vagal synapse. 2) After a fatty or protein meal given together with ethanol, the pancreatic secretion is increased compared to control animals. This increase is considerable for proteins and moderate for water and bicarbonate. In addition, the intraduodenal infusion of oleic acid increases the pancreatic secretion of enzymes six times more in the one-year-alcoholic dog than in control animals (31). This is interpreted as the result of increased release of CCK-PZ, a mechanism recently verified by determining circulating CCK-PZ by its effect on rabbit gallbladder.

It is generally accepted (32, 33) that in nonalcoholic dogs, the contact of ethanol with gastric mucosa releases gastrin. Moreover, Trefot et al (34) have shown that in chronic alcoholic dogs, ingestion of mean and ethanol resulted in greater release of radioimmunologically estimated gastrin than in controls, since gastrin in the dog induces an ecbolic pancreatic secretion, its increased release probably plays a role in the increased secretion of proteins after a meal in chronic alcoholic animals. In fact, it has been recently shown by Palasciano et al (35) that the increased release of CCK-PZ plays a much more important role than increased release of gastrin in this response.

Changes in secretin release has not been studied in chronic alcoholic dogs, but very probably, they are less important than the alterations of CCK and gastrin release.

In a recent unpublished work, our chronic alcoholic dogs and their control dogs have been restudied at the end of two years of alcohol consumption. Under a prolonged perfusion of secretin (1 C U/Kg/h), flow rate and bicarbonate output are significantly increased in the alcoholic group compared to controls, protein output being significantly reduced and protein concentration not significantly modified. This is in agreement with the work of Tasso et al (36) and of Dreiling et al (37), showing that the mass of ducts was increased both in chronic alcoholic rats as well as in patients with chronic calcifying pancreatitis. Moreover, dose response curve of secretin alone (0.5 to 8.0 U/Kg/h or of secretin (1 C U/Kg/h) + CCK (1.5 to 24.0 U/Kg/h) indicate increased sensitivity of the parenchyma.

The most dramatic two-year change of secretory pattern of chronic alcoholic dogs is the response to intraduodenal injection of oleic acid. The protein output of the pancreatic juice is increased threefold above matched controls.

In conclusion, these data show that in chronic alcoholic dogs, the consumption of ethanol, fat and proteins increases by different mechanisms the concentration of proteins in pancreatic juice, and favors the precipitation of these proteins, a situation comparable to that seen in chronic calcifying pancreatic patients, where there is an overconsumption of ethanol, fat and proteins.

5. In the rat, it had been shown that the consumption of ethanol was associated with increased concentration of proteins in pancreatic juice. The transit time of newly synthetized exportable proteins in the acinar cell of these alcoanimals studied recently by the methods of DeCaro and Palade (38), is significantly decreased. This corresponds to what is observed when the animal is given cholinergic drugs or CCK stimulation. These studies suggest that the pancreas of chronic alcoholic rat behaves similarly to that of the chronic alcoholic dog. Further investigations with alcoholic rats reveal that administration of ethanol results in increased and prolonged secretion of protein by the pancreas (39).

One sees that the secretion of proteins by the pancreas is increased in the chronic alcoholic rat after meal or ethanol ingestion as it is in the alcoholic dog. A final link in the chain would be the demonstration of increased biosynthesis of pancreatic excretory proteins in chronic alcoholic animals. Sardesai and Orten (40) found a significant decrease of the biosynthesis of pancreatic proteins following carbamylcholine stimulation after 30 weeks of alcohol consumption. The results of Orrego-Matte et al (41), and of Decloitre et al (42) could be interpreted in the same way. Perhaps the discordance can be explained by a delayed increase in biosynthesis in alcoholic animals, a possibility suggested by Webster et al (43). But we are now studying the protein biosynthesis later after food intake. It is in effect possible to assume that in the alcoholic rat, the increase of biosynthesis is delayed compared to nonalcoholic controls.

Conclusion

Data have been presented from human experimental findings, suggesting that the first lesion of alcoholic pancreatitis is obstruction of the ducts by precipitation of a normal protein within a hyperconcentrated pancreatic juice.

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Small Bowel Structure and Function in Pancreatic Steatorrhea*

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Introduction

It has, until recently, been generally accepted that the exocrine secretions of the pancreas are concerned almost exclusively with the digestion of carbohydrates, fats, and protein to a form which permits these basic foodstuffs to be assimilated for absorption by the small bowel mucosa.

It now seems possible that pancreatic enzymes may have more complicated and diverse functions as well. Recent studies suggest that these enzymes may have a trophic effect on the small bowel mucosa, increasing both villous height and absorptive capacity (1). It also seems probable that the concentration of intraduodenal enzymes may auto-regulate the release of the gut hormones secretin and cholecystokinin and that this "feedback inhibition" does not occur in chronic pancreatitis (2).

In addition, there have been increasing reports and speculation regarding the role of pancreatic exocrine secretions in vitamin B_{12} (3–7), iron (8–12) and free fatty acid (3, 13) absorption and possibly impaired intraduodenal micellar formation or bile salt stability in pancreatic lipase deficiency.

These observations, apart from suggesting newer physiologic functions of pancreatic secretion, are of obvious importance with regard to the differential diagnosis between pancreatic and other forms of steatorrhea.

To assess whether the tests conventionally regarded as indicating intestinal malabsorption may be disturbed in the maldigestion of pancreatic steatorrhea, direct and indirect tests of small bowel function and structure were carried out in a group of patients with pancreatic steatorrhea.

Material

One or more of the conventional tests of small intestinal function was carried out on 60 patients with steatorrhea caused by inflammatory disorders of the pancreas. Radiologic evidence of calcification of the pancreas was present in 50 patients, and a further 5 had surgical or necropsy confirmation of the disease. Of the remaining 5 patients, 4 had experienced recurrent acute episodes of pancreatitis associated with "pancreatic diabetes" and biochemical evidence of gross pancreatic insufficiency as determined by the secretin-

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pancreozymin test, and one patient had all the characteristic clinical stigmata of adult fibrocystic disease including bronchiectasis, clubbing, and a positive sweat test. Histologic or clinical evidence of cirrhosis of the liver was uncommon in the patients with calcific pancreatitis, only 4 showing early cirrhosis on routine liver biopsy. Pancreatic function, as measured by the response to secretin and pancreozymin, was grossly impaired in all but 2 of the 60 patients. Alcohol was the major etiologic factor in no less than 48 patients; 2 had been operated on for biliary disease; one had fibrocystic disease; and the etiology was uncertain in nine.

Fifty-four patients gave a characteristic history of steatorrhea which was confirmed by radiotriolein and chemical stool fat analysis; and 6 patients had biochemical evidence of steatorrhea without a definitive clinical history. Clinically, 10 patients passed frank oil in their stool and a further 22 required replacement therapy to control the diarrhea.

Methods

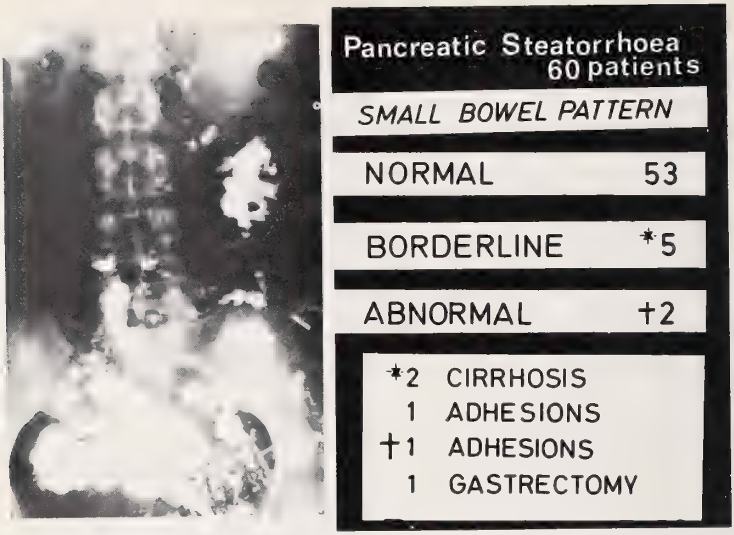
The following tests of small bowel function and structure were carried out in patients with pancreatic steatorrhea:

1. A barium meal follow-through using nonflocculating barium
2. *Fat Absorption:* was measured by the I^{131} triolein and I^{131} oleic acid and chemical fecal fat analysis on a daily diet of 70–150 gram of fat
3. A 2-hour glucose tolerance test
4. *Xylose Absorption*
5. *Vitamin B_{12} Absorption:* (Schilling test)
6. *Urinary Indican* excretion in 24 hours
7. The gastrointestinal loss of protein
8. *Jejunal Biopsies* were carried out with the Crosby capsule
9. A series of indirect blood tests of small bowel function including serum proteins, cholesterol, calcium, iron, B_{12}, folate, and the prothrombin index.

Where abnormal tests were found, the tests were repeated after the administration of intrinsic factor, antibiotics, sodium bicarbonate, or whole pancreatic extract. In addition, the effect of near total dietary fat restriction (5 grams fat/day) was tested on selected patients.

Results

Barium meal studies (Fig. 1): A barium meal follow-through examination of the small bowel was carried out in 60 patients. Two of the 60 patients examined had an abnormal small bowel pattern with clumping and segmentation of the barium. One of the patients had intraabdominal adhesions and the other had previously had a gastrectomy. A further 5 patients had borderline abnormalities of the small bowel with evidence of hypermotility and minimal clumping; and of these, two had associated hepatic cirrhosis and one had adhesions from previous abdominal surgery. Other parameters of small bowel function and structure in these 7 patients were largely normal, the only



Pancreatic Steatorrhoea
60 patients

SMALL BOWEL PATTERN	
NORMAL	53
BORDERLINE	*5
ABNORMAL	†2

*2	CIRRHOSIS
1	ADHESIONS
†1	ADHESIONS
1	GASTRECTOMY

FIG. 1. Small bowel radiology in pancreatic steatorrhea.

abnormality being a low xylose absorption in one patient. In none of the 60 patients was dilatation of the small bowel noted.

Fat absorption: Dual tests of fat absorption using radioisotope techniques were carried out on 14 patients with pancreatic steatorrhea. On the first occasion a radioiodinated triglyceride (I^{131} triolein) was used and the test was then repeated with a radioiodinated free fatty acid (I^{131} oleic acid). Stools were collected for 5 days after the administration of a capsule containing 25–100/uc of the respective isotope and the radioactivity found in the stools was expressed as a percentage of the administered dose.

Figure 2 shows the results of the stool radioactive fat excretion in 9 patients with calcific pancreatitis and in 5 with noncalcific pancreatitis. Three of the 14 patients had a markedly elevated fecal radioactivity after I^{131} oleic acid, and two had minimally elevated levels. It is of interest that the three patients with markedly elevated levels had gross steatorrhea as evidenced by radiotriolein excretion levels exceeding 35% of the administered dose and chemical stool fat levels greater than 25 gram/day.

Of the 5 patients with abnormal I^{131} oleic acid excretion, a xylose absorption test was normal in the 3 in whom it was performed, two had a normal jejunal biopsy and one had partial villous atrophy. The Schilling test was normal in one patient and in the other tested showed a poor Co^{57}B$_{12}$ uptake on four separate occasions. On the other hand, of the 9 patients with normal radiooleic acid absorption one absorbed xylose poorly and one had a poor B$_{12}$ uptake.

Glucose tolerance test (Fig. 3): A two-hour glucose tolerance test after a 50 gram oral dose was carried out on all the 60 patients with pancreatic steatorrhea. Thirty-six of the 60 patients were either overt diabetics on insulin or oral hypoglycemic agents when first seen or have since become frankly

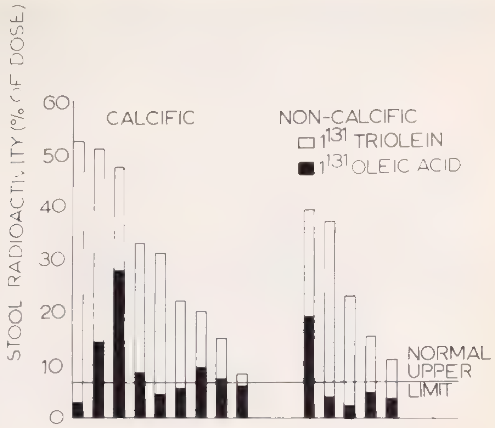


FIG. 2. Dual isotopically labeled fecal fat excretion in 14 patients with pancreatic steatorrhea.

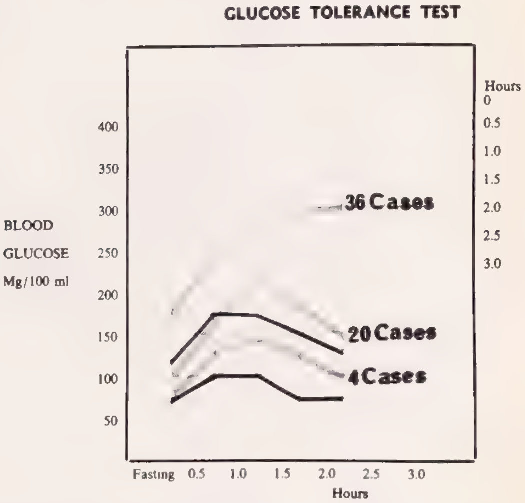


FIG. 3. Glucose tolerance tests in 60 patients with pancreatic steatorrhea.

diabetic. A further 20 had a frankly diabetic or abnormal glucose tolerance test and only 4 had normal glucose tolerance tests. None of the patients showed the flat type of glucose tolerance curve associated with small bowel malabsorption.

Xylose absorption: D- Xylose absorption was measured in 51 of the 60 patients with pancreatic steatorrhea. Figure 4 shows the results of the 5-hour urinary excretion of D-xylose after a 25 gram oral load in 41 patients with calcific pancreatitis and 10 with noncalcific pancreatitis. Fifteen patients with chronic pancreatitis but without steatorrhea are included for comparison. Seven of the 51 patients (13.7%) with steatorrhea excreted less than 4.3 gram in 5 hours. Two of these had histologic cirrhosis of the liver in which xylose tolerance may be impaired, leaving a corrected incidence of 10% with impaired xylose absorption due to the pancreatic steatorrhea alone. None of the 15 patients free of steatorrhea showed any defect in xylose absorption. All 7

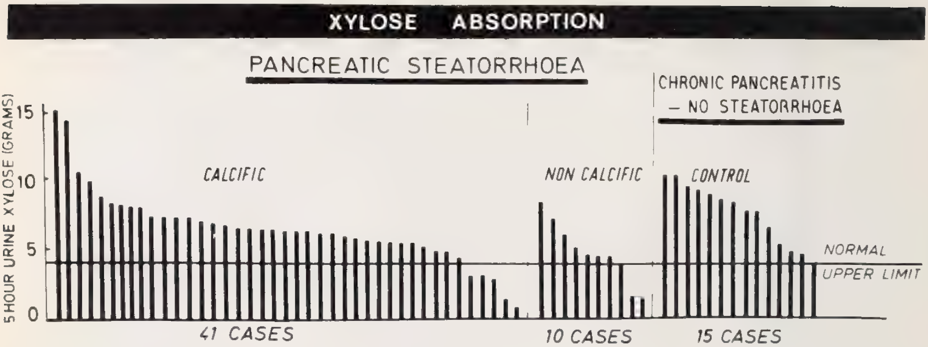


FIG. 4. Xylose absorption in 51 patients with pancreatic steatorrhea and 15 patients without steatorrhea.

patients demonstrating impaired xylose absorption had a normal $Co^{57}B_{12}$ uptake, 6 had a normal jejunal biopsy; and 1 showed partial villous atrophy. The low xylose excretion was corrected by prior viokase administration or a virtual fat-free diet in 2 patients so tested.

Vitamin B_{12} uptake: A 24-hour urinary excretion of $Co^{57}B_{12}$ (Schilling test) was carried out in 52 of the 60 patients with pancreatic steatorrhea.

Figure 5 shows the results obtained in 41 patients with calcific pancreatitis and 11 with noncalcific pancreatitis. Sixteen patients with chronic pancreatitis but without steatorrhea are included for comparative purposes.

Four of the 52 (8%) patients excreted less than 3% of the administered dose of $Co^{57}B_{12}$ in 24 hours. A further 13 (30%) patients excreted between 3 and 8% in 24 hours, but it should be noted that 3 patients without steatorrhea also had levels of this order.

Figure 6 shows the results of repeat tests of $Co^{57}B_{12}$ excretion in 8 patients and the effect of intrinsic factor, viokase, and sodium bicarbonate on the 24 hour urinary excretion of the isotope. Although there was a fairly wide variation in the results when the test was carried out on different days the patients with a normal result on the first test remained normal and those with diminished $Co^{57}B_{12}$ absorption remained low. Intrinsic factor did not increase the 24 hour urinary excretion of $Co^{57}B_{12}$, while pancreatic extracts (viokase) and sodium bicarbonate appeared to increase vitamin B_{12} uptake in the patients tested, although the level was not returned to complete normality in any of the patients.

Improvement of the steatorrhea by a 5 gram fat diet markedly improved B_{12} uptake in 2 patients tested. Of the 4 patients with very low $Co^{57}B_{12}$ uptake levels, all 4 had a normal xylose absorption and barium meals, 3 had a normal jejunal biopsy, and one had partial villous atrophy. The I^{131} oleic acid excretion was abnormal in the one patient tested. An augmented histamine test was carried out in the majority of the patients and achlorhydria was not encountered. The pH of the duodenal fluid was measured in two patients one of whom showed consistently low pH levels in the juice. Sodium bicarbonate improved B_{12} absorption in this one patient but did not return the $Co^{57}B_{12}$

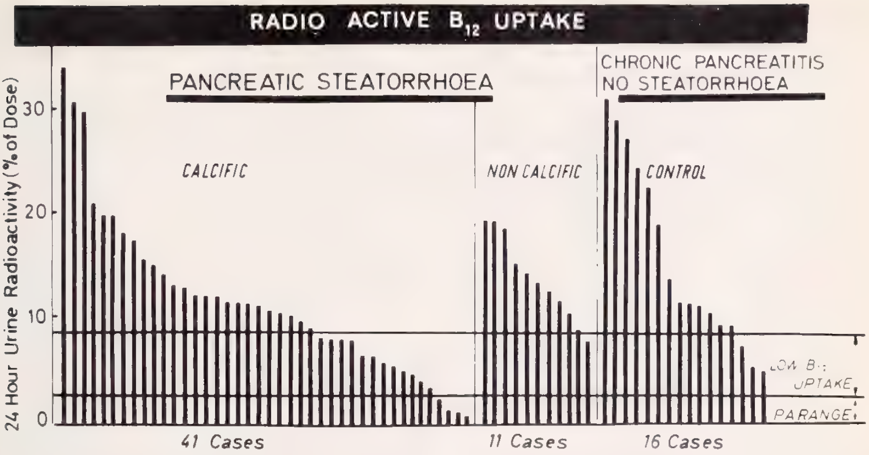


FIG. 5. Radioactive B_{12} excretion per 24 hours in 52 patients with pancreatic steatorrhea and 16 patients without steatorrhea.

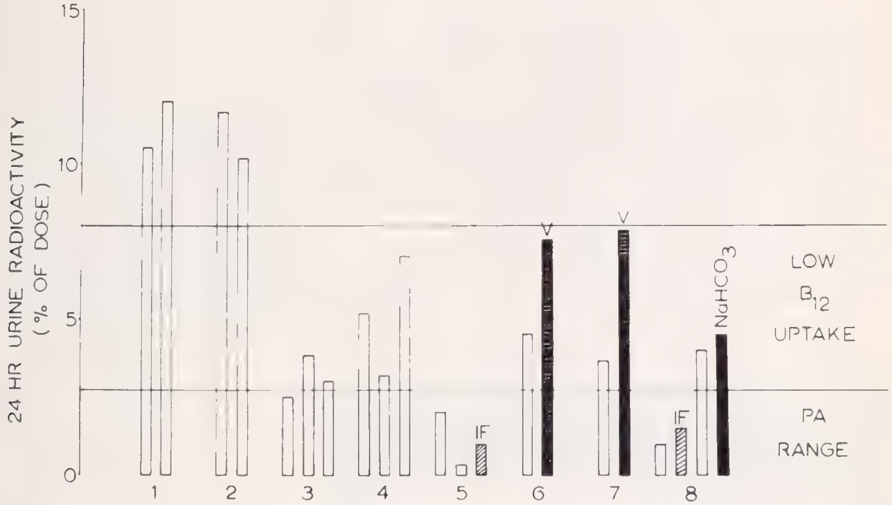


FIG. 6. Repeat vitamin B_{12} uptake studies in 8 patients—the effect of intrinsic factor, bicarbonate and viokase on the 24-hour urine radioactivity: IF Intrinsic factor and V viokase.

excretion to complete normality. Parietal cell and intrinsic factor antibodies were absent from the sera in the patients with low B_{12} absorption.

Urinary indican: The excretion of indican in the urine was measured in 24 patients as an indirect indication of small bowel bacterial overgrowth. The urinary indican levels in these patients (48 ± 32 (SD) mg/24/h) was similar to that of an adult control group (49 ± 24 (SD) mg/24/h). There did not appear to be any correlation between the indican levels and the severity of steatorrhea as measured by a 5-day fecal fat. For example, one patient with an indican level of 8.5 mg/24 hrs had a fecal fat of 11 gm/24 hrs, another with an indican of 87 mg/24 hrs had a fecal fat of 6 gm/24 hrs, while a third with severe oily steatorrhea of 60 gm/24 hrs had an indican of 64 mg/24 hrs. Only one patient had an abnormally high indican level (<100 gmg/24 h).

Small bowel histology: Peroral jejunal biopsies were carried out in 38 patients. Nearly all the biopsies were taken from patients with calcific pancreatitis. Figure 7 shows the jejunal biopsy findings in the 38 patients and these have been compared to the findings in 20 patients with chronic pancreatitis but free of steatorrhea.

Total villous atrophy was not found in any of the specimens examined and the mucosal morphology was completely normal in the vast majority of patients. In addition, there did not appear to be an increased villous height when compared to controls. Four patients with pancreatic steatorrhea had mucosal changes which could be regarded as mildly abnormal. These mucosal changes consisted of villous to nonvillous ratio of less than 1.5:1, which by definition must be regarded as partial villous atrophy. However, even in these, the surface epithelial layer and brush border were normal.

Other changes, of doubtful pathologic significance, were an increased infiltration of cells in the lamina propria, clubbed, branched or fused villi and what appeared to be an excess of goblet cells. Two biopsies showed a dense concentration of hemosiderin at the tips of the villi and both these patients were found to overabsorb radioiron on testing. No villous abnormalities were noted in the patients with chronic pancreatitis but without steatorrhea.

Protein leakage from the gut: To determine whether protein-losing enteropathy may occur in pancreatic steatorrhea, 15–25/uc of Chromium^{51} albumin was administered IV to 14 patients with marked pancreatic steatorrhea and the radioactivity in a 6 day stool collection was measured. The normal upper limit of 1% of the administered dose had previously been determined in control subjects. Thirteen of the 14 patients excreted between 0

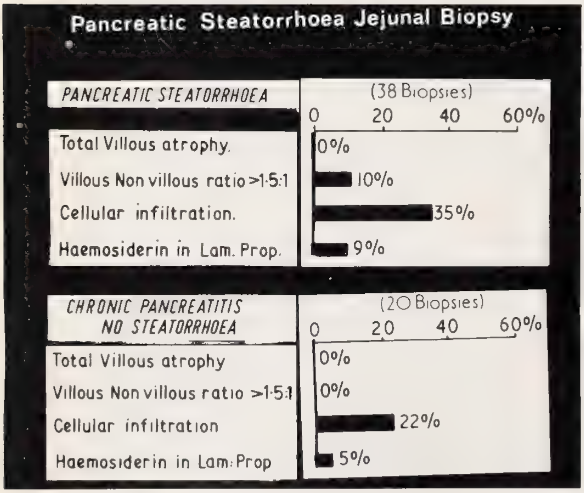


FIG. 7. Jejunal biopsy findings in 38 patients with pancreatic steatorrhea and 20 without steatorrhea.

and 0.7% in the stools and the remaining one excreted 1.1%. This fractionally elevated stool excretion in the latter patient may have been due, in part, to the presence of intraabdominal adhesions developing after distal pancreatectomy.

Jejunal dissacharidase activity: Descending chromatography for the presence of unsplit disaccharides in the stool was carried out in 12 of the 60 patients. The presence of disaccharides was estimated on a qualitative basis. Glucose was a fairly common finding, occurring in 8 patients, one showed the presence of sucrose and another the presence of maltose. Lactose was not found in any of the stool samples tested.

The jejunal mucosal disaccharidases, sucrase, maltase and lactase, were determined quantitatively in 20 patients with pancreatic steatorrhea and the results were within the normal range in all.

Indirect Tests of Small Bowel Function

During the direct investigation of small bowel function, serum was taken from the patients for the evaluation of blood tests conventionally carried out in patients with small bowel dysfunction to assess the absorptive capacity of the gut for proteins, fats, minerals and vitamins. The indirect tests of small bowel function consisted of serum proteins, serum cholesterol, serum calcium, serum iron, prothrombin index, serum B_{12} and serum folate.

(a) *Serum proteins:* The serum albumin and globulin was determined in all of the 60 patients with pancreatic steatorrhea. Hypoalbuminemia and hyperglobulinemia were relatively common findings even in the absence of liver cirrhosis. Five of the 60 patients (8%) had serum albumin levels below 3 grams % and a further 10 showed albumin levels between 3 and 4 grams%. Only 3 of these 15 patients had cirrhosis of the liver.

The serum globulins were markedly elevated ($<$ 4 gram.%) in 12 of the 60 patients (20%)—one of whom had cirrhosis of the liver—and a further 8 showed moderate hyperglobulinemia, with serum globulin levels ranging from 3 to 4 grams%.

Serum electrophoresis was carried out in 30 patients without clinical cirrhosis to identify the globulin fraction responsible for the hyperglobulinemia. Thirteen of the 30 patients showed a distinct increase in the gammaglobulin fraction; the other fractions being normal. The increase was found to be of the IgA + IgG fractions on radioimmunoelectrophoresis (14).

(b) *Calcium:* The serum calcium was measured in 58 of the 60 patients with pancreatic steatorrhea. Two patients had a serum calcium level below 9 mg % but the lowest level in these was 8 mg %. The serum phosphorus was normal in the patients showing this mild hypocalcemia. A high alkaline phosphatase could always be attributed to partial common duct obstruction. None of the patients showed clinical or radiologic evidence of osteomalacia or secondary hyperparathyroidism.

Serum cholesterol: Of 53 patients in whom the serum cholesterol was available, 7 showed levels less than 150 mg %. Only two patients had a serum cholesterol level less than 100 mg %. Three of the 7 patients had liver cirrhosis on histology.

Prothrombin index: The prothrombin index was measured in 57 of the 60 patients prior to liver biopsy or surgery. Three patients had a prothrombin index less than 80%. Two had overt manifestations of liver disease and the remaining one had cirrhosis on liver biopsy.

Serum iron, B_{12}, and folate (Fig. 8): The serum iron was determined in 27 of the 60 patients. Three patients had serum iron levels less than the accepted normal range. Very low serum iron values were not encountered. This is of interest as many of the patients were at least 25–30% below their normal weight and malnutrition due to alcohol was not uncommon. Conversely, 8 patients showed serum iron levels greater than the accepted normal range, and 4 of these had very high levels. The effect of chronic pancreatitis on iron absorption is at present controversial (12, 15).

The serum B_{12} was measured in 36 of the 60 patients. None of the patients had serum B_{12} levels of the order usually found in pernicious anemia or prolonged B_{12} malabsorption. One patient had a borderline level of 195 pg/ml but in him the $Co^{57}B_{12}$ absorption test was normal. Nine patients had vitamin B_{12} levels exceeding 1,000 pg/ml in the absence of liver disease or recent vitamin B_{12} administration. It is of interest that clinical or hematologic evidence of vitamin B_{12} deficiency was not encountered in any of the 60 patients with pancreatic steatorrhea despite the very low vitamin B_{12} uptake in 4 of them.

The serum folate was measured in 35 of the 60 patients with pancreatic

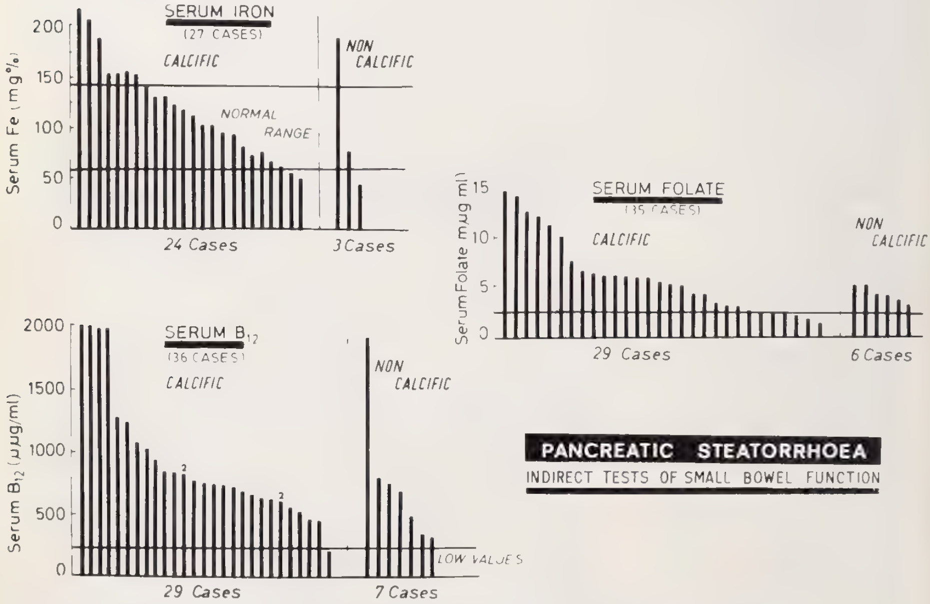


FIG. 8. Serum Iron, B_{12}, and folate levels in pancreatic steatorrhea.

steatorrhea. Two patients had moderately low levels of serum folate, 2.7 ng/ml % and 2.0 ng/ml % respectively. Both patients were severe alcoholics and one had cirrhosis in addition to calcific pancreatitis. Normal serum folate levels were found in the remaining 33 patients, the majority of whom also had alcoholic pancreatitis. Conversely, 5 patients had serum folate levels greater than 10 ng/ml.

Discussion

This study was performed to determine whether the tests in conventional use for the investigation of small bowel function could be abnormal in pancreatic steatorrhea, the reasons for these abnormalities and whether the abnormalities constituted a problem in the differential diagnosis between small bowel and pancreatic steatorrhea.

The results of this study show that certain of the small bowel function tests may occasionally be abnormal in patients with pancreatic steatorrhea. The most common finding was a diminished absorption of D-xylose, 10% of the patients having a markedly low urinary output in the 5-hour period of the test. Grossly impaired absorption of vitamin B_{12} was found in 8% of the patients and 30% had urinary excretion levels compatible with small bowel malabsorption. A few patients with very high chemical fecal fat results exceeding 25 grams per day appeared to handle fatty acids poorly as evidenced by high stool radioactivity after the feeding of radioiodinated oleic acid. Less frequent findings were small bowel radiography which were vaguely similar to those found in malabsorption states, and a small number of patients demonstrated partial villous atrophy of the jejunal mucosa. Total villous atrophy was not found in any of the patients. None of the patients showed protein-losing enteropathy, and the disaccharidase activity of the small bowel mucosa quantitively and qualitatively was unimpaired. As expected, an abnormal or frankly diabetic glucose tolerance test occurred in 93% of the patients. Pancreatic replacement therapy (viokase) and virtual total dietary fat restriction were shown to be the only means by which the B_{12}, xylose, and labeled free fatty acid abnormalities could be improved, but even then not regularly to normal values.

The possible explanation for the abnormalities in the small bowel function studies in pancreatic steatorrhea are uncertain and difficult to explain. Clearly, the first consideration is whether the tests in current usage are reliable and reproducible measures of small bowel absorption. Doubts have been cast on the validity of the I^{131} oleic acid test and the reproductivity of vitamin B_{12} absorption and xylose tolerance tests. While it is agreed that absolute reproducibility is not always achieved, the results of this study indicate that a separation between normal and abnormal values could be attained on successive testing. Consequently the low xylose levels and very low B_{12} uptake found in a number of our patients were consistently low when the tests were repeated. It has been suggested that the high fecal indices found after I^{131} oleic acid administration are due to "agent or agents" missing in the event of pancreatic hyposecretion which are essential for the absorption of fat from the small bowel, and a small bowel absorption defect has been postulated. With regard to the low urinary B_{12} results, a number of theories have been advanced, linking pancreatic secretion with Vitamin B_{12} absorption (12, 16). These include (a) the role of pancreatic enzymes in the formation of the IF-B_{12} complex, (b) impaired binding of IF-B_{12} complex to intestinal receptor sites in pancreatic insufficiency, (c) excess intraduodenal acid may separate the bound IF-B_{12} complex, (d) the fact that pancreatic enzymes facilitate dimerization of IF, (e) the possibility of a "releasing factor" in pancreatic juice at the ileal brush border, (f) bacterial competition for intraluminal B_{12}, (g) adsorption of B_{12}-IF to intraluminal components, and (h) the fact that the low intestinal pH resulting from impaired bicarbonate secretion in pancreatitis may interfere with Vitamin B_{12} absorption. It is of interest that despite the low uptake, serum B_{12} levels were nearly always normal and anemia exceedingly rare. It has been shown that none of the above theories adequately explains the impaired B_{12} uptake (17).

A number of diverse effects have thus been demonstrated in this study. On the negative side are: (1) The infrequency of the small bowel abnormalities and their finding in only a small group of patients despite gross pancreatic insufficiency in the remainder; (2) The finding of these abnormalities in only a few patients with steatorrhea despite equally severe pancreatic enzyme deficiency in other patients without steatorrhea; (3) The fact that the abnormalities tend to be isolated and rarely occur together in the same patient; (4) The normal small bowel mucosa and disaccharidase activity even in patients with gross steatorrhea and demonstrable B_{12}, xylose, or fatty acid abnormalities; (5) The inability to correct the abnormalities by the administration of antibiotics or calcium supplements and the finding of a normal urinary indican excretion suggests that there is no significant bacterial overgrowth or ileal calcium deficiency in the small bowel in cases of pancreatic steatorrhea; and (6) The maintenance of duodenal pH in the region of 6 after test meals despite gross pancreatic bicarbonate deficiency and the relative inconsistency of sodium bicarbonate to restore the abnormal B_{12}, xylose, and fatty acid results to complete normality.

Perusal of the literature in combination with the present results leaves only two aspects on the positive side: (1) pancreatic replacement therapy appeared to be the only substance which could consistently restore the B_{12}, xylose, or fatty acid values from abnormal to normal or near normal values(13, 18) and (2) total dietary fat restriction (to ± 5 gram fat/day) which restored the fecal fat to normal in previously grossly steatorrheic patients, resulted in improvement in the B_{12} and xylose results in the patients tested. It seems therefore, that the abnormality is linked with the presence of the steatorrhea and not an absorption defect at the small bowel mucosal surface. It would be wrong to term the abnormalities as mucosal malabsorption but rather as intraluminal defects of absorption. The answer may simply be a physical one with a "slip-stream" effect—the test substance making poor contact with the absorbing surface of the bowel due to a greasing effect of the mucosa by the oily nature of the unsplit fat in the lumen of the bowel. Clearly this does not explain why the small bowel tests should be abnormal only in a minority of the patients. Alternatively, the defect may be associated with impaired micellar formation or bile salt function. However, the latter studies have to be tested since little is known of the effects of conjugated or unconjugated bile salts on B_{12} or xylose uptake.

Although the mechanisms of the abnormalities in small bowel function remain unclear, they do not seem to pose a great problem in the differential diagnosis between pancreatic and small bowel steatorrhea. Firstly, the abnormal results were nearly always isolated findings and it was rare to find more than one abnormality in any one patient. There was only one patient who exhibited more than one abnormality and the finding of two abnormalities suggested the presence of associated disease, e.g., gastrectomy, cirrhosis and, most important, the development of abdominal adhesions due to recurrent attacks of pancreatitis or previous abdominal surgery for the pancreatitis. Secondly, the typical history of painful alcohol-induced gallstone or idiopathic pancreatitis usually leaves one in little doubt that the steatorrhea is pancreatic in origin, particularly as the pancreas will be calcified in most cases, and the finding of oil in the stools in virtually diagnostic of a pancreatic etiology. The only source of confusion may be painless chronic pancreatitis or fibrocystic disease of the pancreas, but in the latter the early age of onset and associated chest disease should be helpful. Thirdly, pancreatic function as tested by secretin-pancreozymin stimulation nearly always shows gross pancreatic enzyme and bicarbonate insufficiency; and, although this type of result may occasionally be encountered in patients with small bowel disease with persistent hypoproteinemia (19), the intensity of the enzyme deficiency does not usually match that found in pancreatic steatorrhea. Finally, the barium studies never showed evidence of small bowel dilatation, total villous atrophy did not occur, and the glucose tolerance test was invariably diabetic or normal in pancreatic steatorrhea and never flat as is common in small bowel malabsorption.

Summary

Small bowel function and structure was investigated in 60 patients with pancreatic steatorrhea. Isolated abnormalities in small bowel function tests, in particular, free fatty acid, xylose absorption and B_{12} uptake were found in a number of patients. A few patients showed barium meal abnormalities and partial villous atrophy of the mucosa and one had an increased urinary indican excretion.

The possible causes and mechanisms for these abnormalities are discussed and it was found that improvement in the steatorrhea by pancreatic replacement therapy or total fat restriction were the only factors which could materially and consistently improve the abnormal tests.

It is suggested that the abnormal tests do not constitute associated small bowel malabsorption but may present a physical defect of absorption due to intraluminal factors associated with the steatorrhea.

A consideration of the history, examination, barium meal, small bowel biopsy and glucose tolerance usually clearly separates small bowel from pancreatic steatorrhea, and the finding of more than two abnormalities in the same patient suggests the presence of associated small bowel disease.

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Techniques and Dosimetry for Inflatable Miniaturized Afterloading in Cancer of the Cervix*

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In this paper we will discuss the techniques and dosimetry in the use of a miniaturized afterloading† device with an inflatable vaginal component, a device and system which we have previously described in principle (1).

Background

For scores of years carcinoma of the cervix of the uterus has been treated with intracavitary applicators of radium which comprise a uterine tube (tandem) and a vaginal device (colpostat). For more than 30 years, the authors have used a modification of the Paris system with a rubber tandem containing radium and a spring separated pair of rubber ovoids, also containing radium. Then, one of us (SMS) devised a mechanical colpostat with more precise control over the separation of the ovoids (2), and subsequently a thin tandem (3) which could be inserted without anesthesia. For many years it had been our custom to insert the Paris type of tandem containing radium with the patient under general anesthesia. During decades of this method of treating cancer of the cervix our survival results, and the severity of our reactions were essentially the same as those reported in most centers. The development of miniaturization of radioactive materials, in our case Cesium-137, made it possible to fashion a tandem so thin it could be inserted into the uterine cavity without anesthesia and it could be afterloaded.

An inflatable spacer between two attached ovoids provided a semi-fixed relationship to the tandem, constant separation of the ovoids, and tolerance of the system by the patient. As previously reported (4), this afterloaded inflatable system has the following advantages:

1. decreased radiation exposure to personnel;
2. substitution of the safer Cesium-137 for radium;
3. more accurate placement;
4. improved tolerance by patients; and
5. disposability of applicators.

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† Afterloading is the insertion of hollow tubes in the patient, and the subsequent loading of these tubes with radioactive material after the patient is in her hown room, thus reducing radiation exposure to personnel.

Requests for reprints should be sent to: Dr. Norman Simon, Radiation Research Office, 19 E. 98 Street, Room 4G, New York, N. Y. 10029.

Description of Applicators

All of the hollow tubing and receptacles in this system have an internal diameter of 1.25 mm. Steel tubes or wire may be inserted, either as a nonradioactive dummy, or as an actual holder for the radioactive sources into the hollow plastic tubing.

The tandem is a semi-malleable thin-walled steel tube with an external covering of plastic and overall diameter of 3 mm. The length of the tandem is 30 cm, standard for the overall length of all tubing used in this system. The end that goes into the uterine cavity is malleable for 6 cm, permitting gentle curves with a radius of no less than 8 cm. A rubber stop 1 cm in diameter, shaped like a conventional cork, encircles the tandem and can be adjusted to the length of the uterine cavity and rests against the cervix when the tandem is inserted into the uterus. Within the tandem is a dummy wire, 1.25 mm in diameter, the same thickness as the subsequently loaded source holder.

The vaginal applicator is composed of a plastic "doughnut" 4 cm in outer diameter, inflatable and semi-flexible. The walls of the doughnut are of polyvinyl chloride plastic .25 mm thick. The "hole" in the doughnut is 1 cm in diameter and on inflation, holds the cervical stop tightly around the tandem.

In the circumference of the doughnut there are lappets of plastic to which the ovoids are attached and held by the afterloading tubes that fit in these lappets (Fig. A). The ovoids are of silicone rubber, and they are designed to simulate the size, shape and hardness of rubber Manchester ovoids. Each ovoid contains three afterloading tubes and three radiopaque markers. The afterloading tubes hold the ovoids to the periphery of the doughnut which provides the proper spacing between the ovoids. The doughnut has a separate soft plastic tube, with a conventional syringe adapter on it for inflation after insertion into the vault of the vagina.

The afterloading tubes are 2 mm in their outer diam, and their internal diam is sufficient to accommodate the insertion of 1.25 mm steel tubing the equivalent of 18-gauge French hypodermic needle stock. These afterloading tubes can be readily inserted into or removed from the ovoids. Also, the afterloading tubes can be slid back and forth in the lappets of the ovoids, maintaining an appropriate asymmetrical position if the anatomy requires. The hub of each afterloading tube, and that includes the tandem, has a lock (Luer in type) for rapid and positive fixation of the radioactive source holders in the afterloading tube.

The radioactive sources are non-leachable high specific activity Cesium-137, 10 mg of radium equivalent per cm, sealed within a 1.25 mm (outer diameter) steel tube (18-gauge French needle stock). The holder of this radioactive material is 30 cm in length and the radioactive material is at its tip. At the holding end there is a handle which permits fixation in the Luer lock. There is a triple-color-coded designation on the handle to indicate the activity, active length, and year of manufacture of the source.

Although there is considerable potential for variation in the selection of sources, we have standardized ours to 10 mg of radium equivalent in

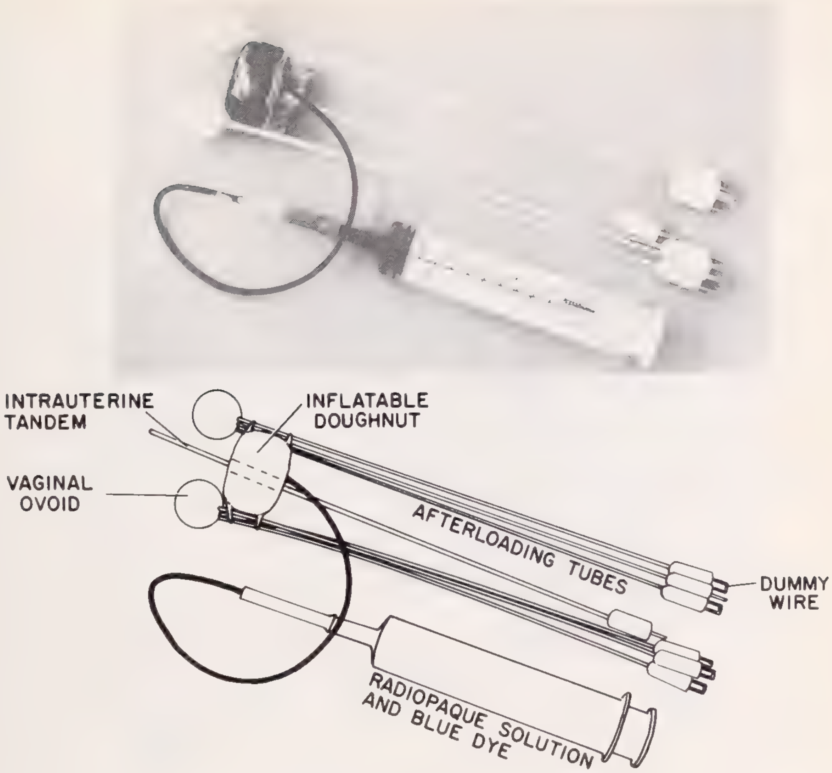

Fig. A

Cesium-137 (10 mg Ra eq ^{137}Cs) for all of our sources except the tandems. Even in the tandems the activity is 10 mg Ra eq ^{137}Cs in each cm. Thus a tandem of 6 cm active length contains 60 mg Ra eq ^{137}Cs, while a tandem 4 cm long contains 40 mg Ra eq ^{137}Cs. For each ovoid, there are three sources, each 1 cm in active length, containing 10 mg Ra eq ^{137}Cs.

It is important to note that this system is also compatible with our previously reported (5) afterloading Heyman applicators in which the same sources used in the ovoids for cancer of the cervix, as above described, can also be used for loading the intrauterine capsules. The afterloading capsules have bulbous plastic tips on the afterloading tubes. The inflatable doughnut holding the ovoids is also useful as a vaginal packing with the afterloading Heyman applicators.

The shield for the radioactive source carriers is a relatively small lead cylinder encased in steel, measuring 27 cm in diameter and 23 cm in height, surmounted by a narrower cylinder 6.3 cm in diameter and 15 cm in height, total weight approximately 100 Kg. This lead safe is imbedded in a mobile afterloading station (Fig. B) which contains instruments, safe and sources, and a shield for physicians and nurses attending the patient. When this shield contains as much as 200 mg Ra eq in ^{137}Cs, the dose of radiation on its surface

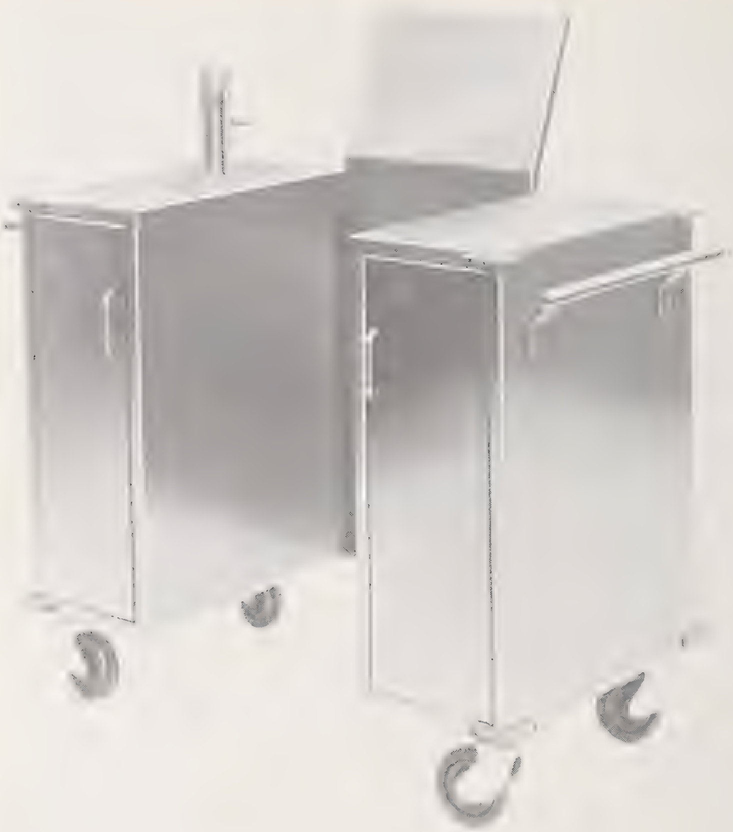

FIG. B

is less than 1 mR/hr. The exposure dose rate behind the shield where the physician or nurse stands is less than 4 mR/hr when the patient has 100 mg Ra eq ^{137}Cs in the uterus.

Technique

The patient is prepared preoperatively with sedation (e.g., barbiturates or Valium®). She is placed in lithotomy position, and the urinary bladder is catheterized with an indwelling Foley catheter, 16 French with a 5 ml bag. The bag of the Foley catheter is inflated with a presupplied mixture of a visible blue dye, and radiopaque material for its identification in subsequent radiographic films.

The anterior lip of the cervix is grasped with a tenaculum, the os is identified, and the uterine cavity is sounded for measurement of its length and for estimation of its position and direction. The afterloading tandem with appropriate curvature is then inserted into the uterine cavity. A metallic seed is implanted into the cervix at a known site, usually 1 cm deep, 1 cm from the tandem in the 3 o'clock position as the operator looks at the cervix. Then the deflated doughnut is inserted over the tandem, the ovoids are adjusted into the fornices, and the doughnut is then inflated with 20 ml of the same mixture used for the bag in the Foley catheter. Ordinarily, no further packing is required. Digital rectal examination assures appropriate position of the ovoids. The protruding ends of the plastic afterloading tubes and the tandem are taped to the inner aspect of the patient's thigh and the patient is now ready for x-ray films of the pelvis to verify and record the appropriate positioning of the device. The metallic seed in the cervix and radiopaque markers in the ovoids help to identify the position of the ovoids to assure their location on either side of the cervix. Radiographic x-ray films in lateral and frontal projections are of value in this "eyeball" determination of appropriate position. The dummy wires in each afterloading tube are identified in the films.

In the event that a complete dose distribution is desired, suitable films for computer input may be made. In our department a pair of stereo shift films in frontal projection provide appropriate input data, but orthogonal films are also useful.

The actual loading of the radioactive material into the afterloading tubes is done in the patient's room. The procedure takes only a few minutes and causes no discomfort to the patient. The radiotherapist removes the dummy wires from each of the afterloading tubes, and rapidly removes the source holders from the lead shield and inserts them into the afterloading tubes which are taped to the patient's thigh.

The patient and nurses are instructed in precautions during the therapy. The patient is allowed to elevate the head of the bed no more than 45°. She may move from side, but not sit up. A constipating drug is administered (e.g., codeine), and a regular diet is allowed for the few days of the treatment.

At the time of removal of the applicators, first the radioactive source holders are removed and inserted into the lead shield. Then the distending fluid is removed from the inflatable doughnut colpostat and from the Foley catheter. All tubes and ovoids are withdrawn, disposed of, and the patient may get out of bed.

Dosimetry

Any of the usual dosimetry systems with which the radiotherapist is familiar can be used with this inflatable afterloading system. As an example, radiation doses to points A and B may be calculated or derived from available isodose tables. The dose may be specified in mg hours of radium equivalent, if that is the system which the radiotherapist is used to.

Computer readouts have been developed for this inflatable system for details of varied distribution, and illustrations follow. These examples of dose distribution may be used as guides for treatment. The dose distribution around the afterloaded system is shaped like a flattened pear, a distribution which is classic for most radium systems. The flattened pear shape tends to decrease the dose in the anterior rectal wall, the vulnerable organ of damage.

The computerized dose distributions illustrated (Diagrams 1-6) consider the tandem in an "ideal" central position in the pelvis, lying in the axis of the vagina. The ovoids are also symmetrical in the illustrations. When these "ideals" do not exist, the effects of the irregularity of the postitions should be considered, particularly in reference to those who depend on a determination of the dose at point A. This subject will be discussed and illustrated more fully in a publication in preparation.

A usual distribution of sources provides an active tandem length of 6 cm containing 60 mg of Ra eq ^{137}Cs. In the ovoids there are three 10 mg Ra eq ^{137}Cs sources on each side for a vaginal distribution of 30 mg Ra eq in each ovoid (Diagram 2). The computer readout of the distribution of dose around the system indicates that an exposure of approximately 6,000 mg hrs of Ra eq ^{137}Cs gives approximately 6,000 rads at point A and 2,000 at point B.

In the event that the tumor is unilateral, not an unusual circumstance, and

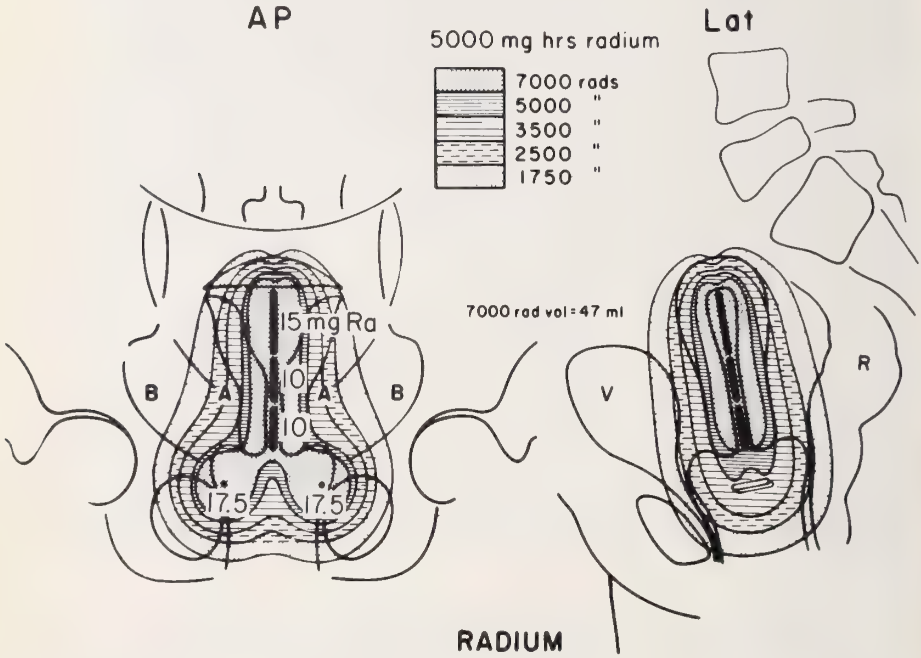

DIAGRAM 1

DIAGRAM 1: This illustration shows a usual and characteristic distribution of isodose surrounding a *radium* intracavitary system. In this instance the tandem contains 35 mg of radium and 2 ovoids each containing 17.5 mg of radium. Points A and B are indicated, as well as the bladder (V) and the rectum (R). The dose distribution for an exposure of 5,000 mg hrs of radium is indicated. The shape of the distribution is the flattened pear. Similarities and differences when cesium is used in the inflatable system will be compared to this "usual" radium dose distribution. All illustrations are normalized to an exposure dose of 5,000 mg hrs of radium or 5,000 mg hrs of radium equivalent ^{137}Cs exposure. The volume receiving 7,000 rads with this exposure dose is included. In the diagram it is to be noted that the radium in the colpostat ovoid is perpendicular to the axis of the radium in the tandem. This is the usual disposition of the vaginal radium in a preloaded system.

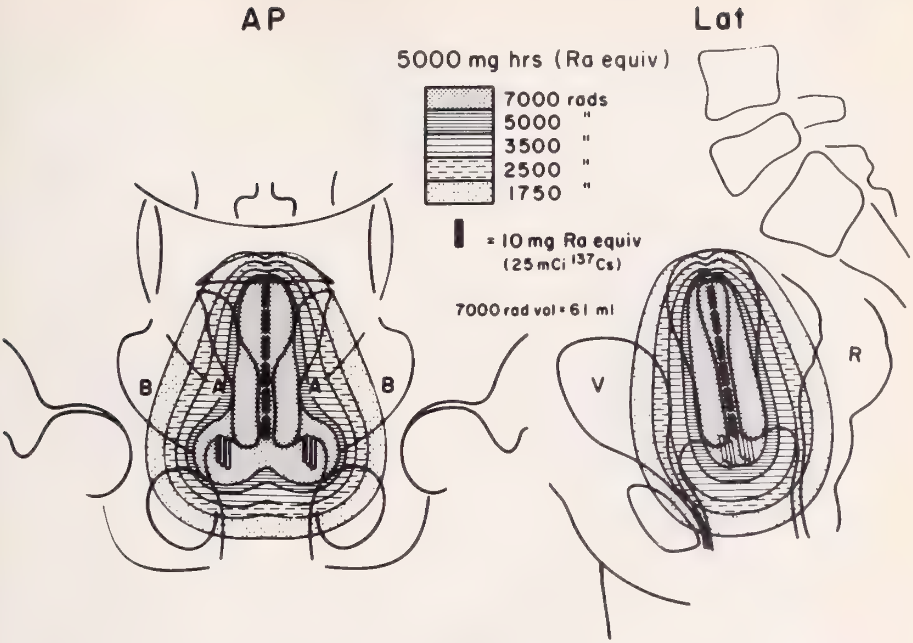

DIAGRAM 2

DIAGRAM 2: In this illustration the tandem contains 60 mg of radium equivalent in ^{137}Cs, and each ovoid in the vagina contains 30 mg of Ra eq in ^{137}Cs. The similarity of the dose distribution, the flattened pear shape, to the distribution with the radium in Diagram 1 is especially noteworthy. In this distribution, an exposure of 5,000 mg hrs Ra eq ^{137}Cs results in an absorbed dose of about 5,000 rads at point A.

an asymmetrical dose distribution is desired, this can be done by unequal loading of the ovoids in the inflatable colpostat (Diagram 3). The illustrations of the computer readouts with these unequal distributions afford an opportunity to tailor the distribution of radiation to the disease (Diagrams 4, 5, 6).

Satisfactory preliminary results, as far as reaction and early response are concerned, have been obtained using the following dose and techniques.

In Stages Ia, Ib, and IIa the intracavitary therapy is of major curative importance. In these cases 6,000 rads is the dose given to point A in a single insertion, 2 to 3 days. In Stages IIb, IIIa and IIIb the dose administered to point A by intracavitary treatment is 4,000 rads, more reliance being placed upon added external radiation.

SUMMARY

An inflatable miniaturized afterloading method of treating cancer of the uterine cervix permits intracavitary radiotherapy without anesthesia and with a short hospital stay. The technique of application applies principles already well known to radiotherapists. The dosimetry follows standard methods, and computer readouts of some detailed dose distributions are illustrated.

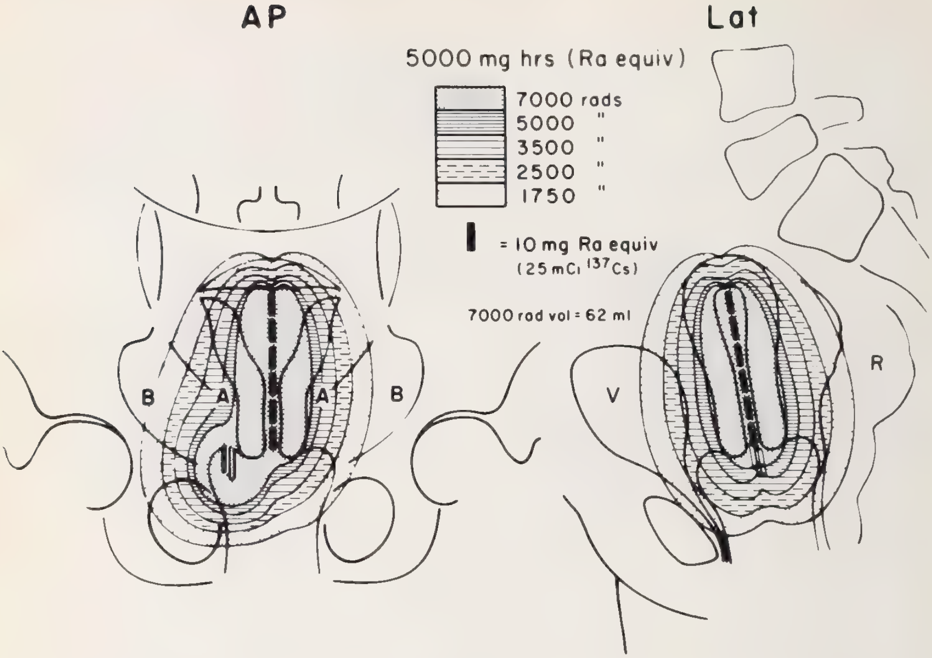
AP
Lat
5000 mg hrs (Ra equiv)
7000 rads
5000 "
3500 "
2500 "
1750 "
= 10 mg Ra equiv
(25 mCi 137Cs)
7000 rad vol = 62 ml
B
A
A
B
V
R

DIAGRAM 3

DIAGRAMS 3, 4, 5, 6: In these diagrams the loading in the vaginal ovoids has been varied. As an example, in Diagram 3 there is no radioactive material in the left ovoid, and 30 mg Ra eq ^{137}Cs in the right, resulting in high radiation dose in the cervix and right vault of vagina. Diagrams 4, 5, and 6 show other variations in distribution.

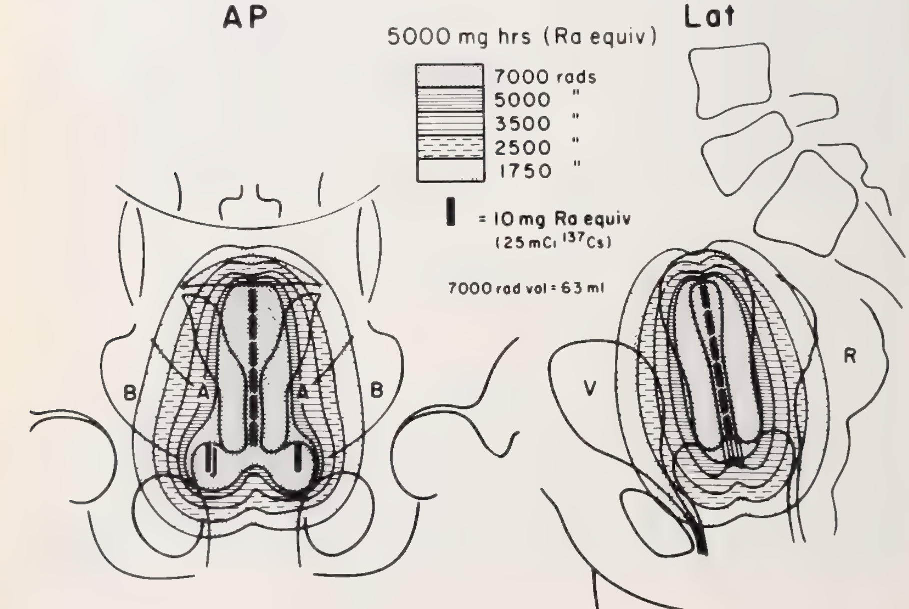
AP
Lat
5000 mg hrs (Ra equiv)
7000 rads
5000 "
3500 "
2500 "
1750 "
= 10 mg Ra equiv
(25 mCi 137Cs)
7000 rad vol = 63 ml
B
A
A
B
V
R

DIAGRAM 4

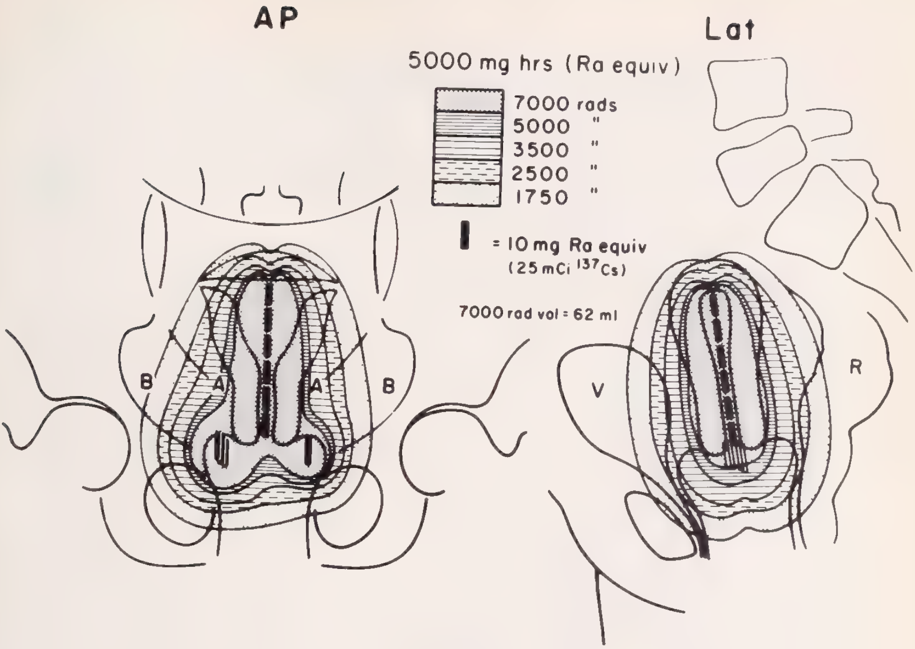
AP
Lat
5000 mg hrs (Ra equiv)
7000 rads
5000 "
3500 "
2500 "
1750 "
= 10 mg Ra equiv
(25 mCi ^{137}Cs)
7000 rad vol = 62 ml
B
A
A
B
V
R

DIAGRAM 5

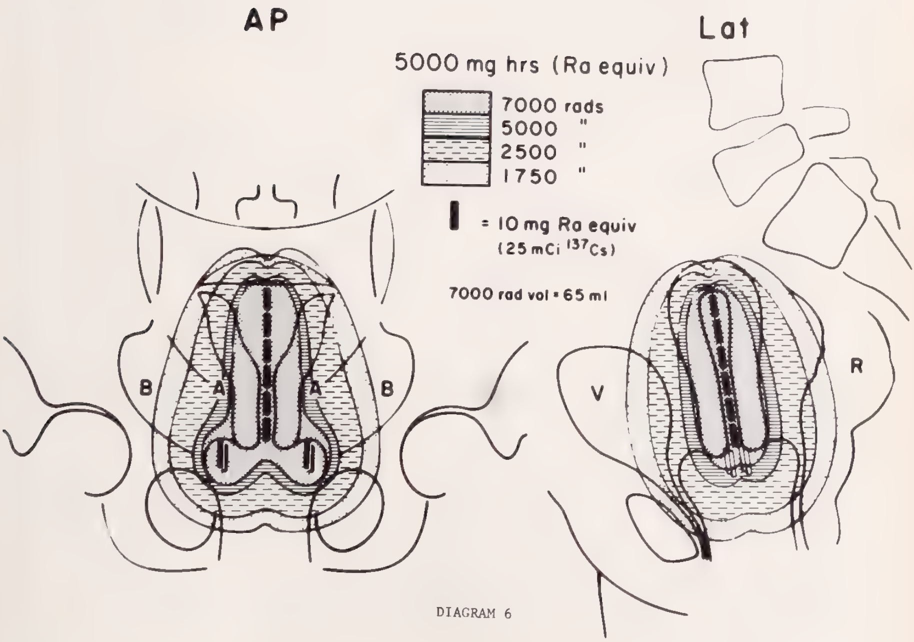
AP
Lat
5000 mg hrs (Ra equiv)
7000 rads
5000 "
2500 "
1750 "
= 10 mg Ra equiv
(25 mCi ^{137}Cs)
7000 rad vol = 65 ml
B
A
A
B
V
R

DIAGRAM 6

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Coxsackie Hepatitis in an Adult, with Ultrastructural Demonstration of the Virus

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Abstract

A 28-year-old man with Coxsackie B virus infection had myocarditis, pericarditis, and myositis. Rising serologic titers to Coxsackie B, types 2 and 5, were documented. The clinical course was complicated by hepatitis, which proved fatal. Liver biopsy prior to clinically obvious hepatitis showed microabscesses. At autopsy evidence of inflammation was present in the heart, striated muscles, and liver. The hepatic tissue obtained at the time of biopsy, when serologic titers to Coxsackie virus were at a peak, was reprocessed for electron microscopy. Particles, identical to those previously documented as Coxsackie virus, were abundant in the liver cells.

Inflammatory liver disease associated with Coxsackie B virus has been demonstrated in experimental animals as a part of a generalized infection (1). Coxsackie virus infection in the human newborn may also be a generalized disease, with hepatic involvement, and may have a fatal outcome (2). A number of investigators have suggested the existence, in the adult, of a hepatitis associated with Coxsackie virus (3–6). The association has not been proven. We studied a patient with clinically documented Coxsackie B infection in whom manisfestations of cardiac and striated muscle involvement were initially prominent, and in whom hepatitis became a significant, and eventually fatal, clinical problem. The etiology of the hepatitis was confirmed by electron microscopic examination of biopsy material.

Case Report

A 28-year-old salesman was first admitted to The Mount Sinai Hospital in October 1972, after three weeks of unexplained fever. He had complained of sore throat and painful swallowing, muscle ache, and general malaise with daily fever elevation to 40°C, as well as occasional sweats. Physical findings at that time included only a mild pharyngitis and a grade i/vi systolic ejection murmur at the left sternal border. The white blood cell count was 18,200 cells/mm^3, with 62% segmented froms, 29% bands, 4% lymphocytes, 2% eosinophils, 2% monocytes, and 1% plasma cells. The hemoglobin was 12.6 G/100 ml, and the hematocrit was 38%. An accumulation of fluid in the pericardial sac and small calcific pulmonary densities were demonstrable on roentgenographs of the chest. The second strength tuberculin (PPD) test gave a positive reaction; however, acid-fast bacilli were not identified in the sputum, urine, or gastric aspirate. The studies for detection of anti-nuclear antibodies, heterophile antibody, and hepatitis-associated antigen, as well as the lupus erythematosus preparation and the latex fixation test, were all negative.

Biopsies of lymph node, bone marrow, and liver were performed. The lymph node showed

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benign hyperplasia, as did the bone marrow. The liver displayed a mild, non-specific inflammation without necrosis. A rising titer of serum antibodies to Coxsackie virus, group B, types 2 and 5, was documented (Table I). Liver biopsy was repeated after 7 days. At this time focal necrosis of individual hepatocytes, with small collections of polymorphonuclear leucocytes, was evident (Fig. 1).

The patient's irregular febrile course continued, with temperatures up to 40°C. A pericardial friction rub was noted. Serial roentgenograms of the chest showed increasing diameter of the cardiac shadow. Pericardiocentesis produced 500 cc of sterile serosanguinous fluid. After large doses of prednisone and solu-cortef, as well as isoniazid, he improved, became afebrile and asymptomatic, and there was no reaccumulation of pericardial fluid. He was discharged with continued corticosteroids (Decadron®), isoniazid, and pyridoxine.

Four weeks later fever recurred, accompanied by diarrhea, with pale stools, dark urine, and an acne-like rash over the arms and trunk. Medication was discontinued without apparent change in his condition. He rapidly developed jaundice. He was somnolent and obviously icteric when readmitted and had a markedly distended abdomen. An enlarged tender liver was palpable 4 cm below the right costal margin. Ankle edema was prominent. His temperature was 102°F. The hemoglobin was 13.5 gm/100 ml, with a hematocrit of 39%. The white blood cell count was 2,700 cells/mm^3. Fibrinogen was 225mg/100 ml, and fibrin split products were not detected. The prothrombin time was 22.8 seconds, with a control of 12 seconds. Glucose was 240mg/100ml and the total serum bilirubin was 11.5mg/100 ml, with a direct component of 10.5mg/100 ml. The determination of serum glutamic oxalacetic transaminase (SGOT) was over 3,000 mu/ml, the serum glutamic pyruvic transaminase (SGPT) was over 1,000 mu/ml, and the alkaline phosphatase was 300 mu/ml. The electrocardiogram and chest roentgenograph were within normal limits. Therapy included parenteral vitamin K, Decadron^{R}, Tylenol^{R}, codeine, and Valium^{R}, as well as keflin and gentamycin. An episode of shortness of breath was accompanied by cyanosis and tachycardia. Heart sounds were distant, blood pressure dropped precipitously and, despite resuscitative efforts, he died.

Necropsy: Major postmortem findings were limited to the heart, striated muscle, lungs, and liver. The pericardium was thickened and extensively adherent to the epicardium, which was covered with fibrous tissue and fibrin. The heart weighed 400 gm and the myocardium was pale, swollen, and firm, with hypertrophy of the left ventricle. Small accumulations of lymphocytes and polymorphonuclear leucocytes surrounded scattered necrotic heart fibers. The striated muscles, which were similarly pale and swollen, exhibited focal fiber necrosis and infiltration with lymphocytes and histiocytes. The severely edematous lungs weighed 1500 gms together.

The liver weighed 2500 gm. The capsule was glistening and tense. Dilated and congested central veins were surrounded by adjacent necrotic hepatocytes, a manifestation of terminal shock. Mid-zonal hepatocytes, however, were swollen and the sinusoids contained scattered lymphocytes and plasma cells, many of which also filled and expanded portal tracts.

Ultrastructural studies: Twenty-micron-thick sections of the second liver biopsy specimen, cut from those areas of the paraffin block with microabscesses, were deparaffinized in cold xylene, rehydrated through graded alcohols, postfixed, dehydrated, embedded in Epon epoxy resin and sectioned and stained with lead citrate for electron microscopy (7, 8). Liver obtained at autopsy,

TABLE I

Antibody titers determined by neutralization test in tissue culture. Significant increments in titers to Coxsackie B2 and B5

	day 6	day 13	day 27
Coxsackie			
B1	1:16	1:16	—
B2	1:256	1:512	1:1024
B3	1:16	1:16	—
B4	1:128	1:128	1:128
B5	1:32	1:128	1:128

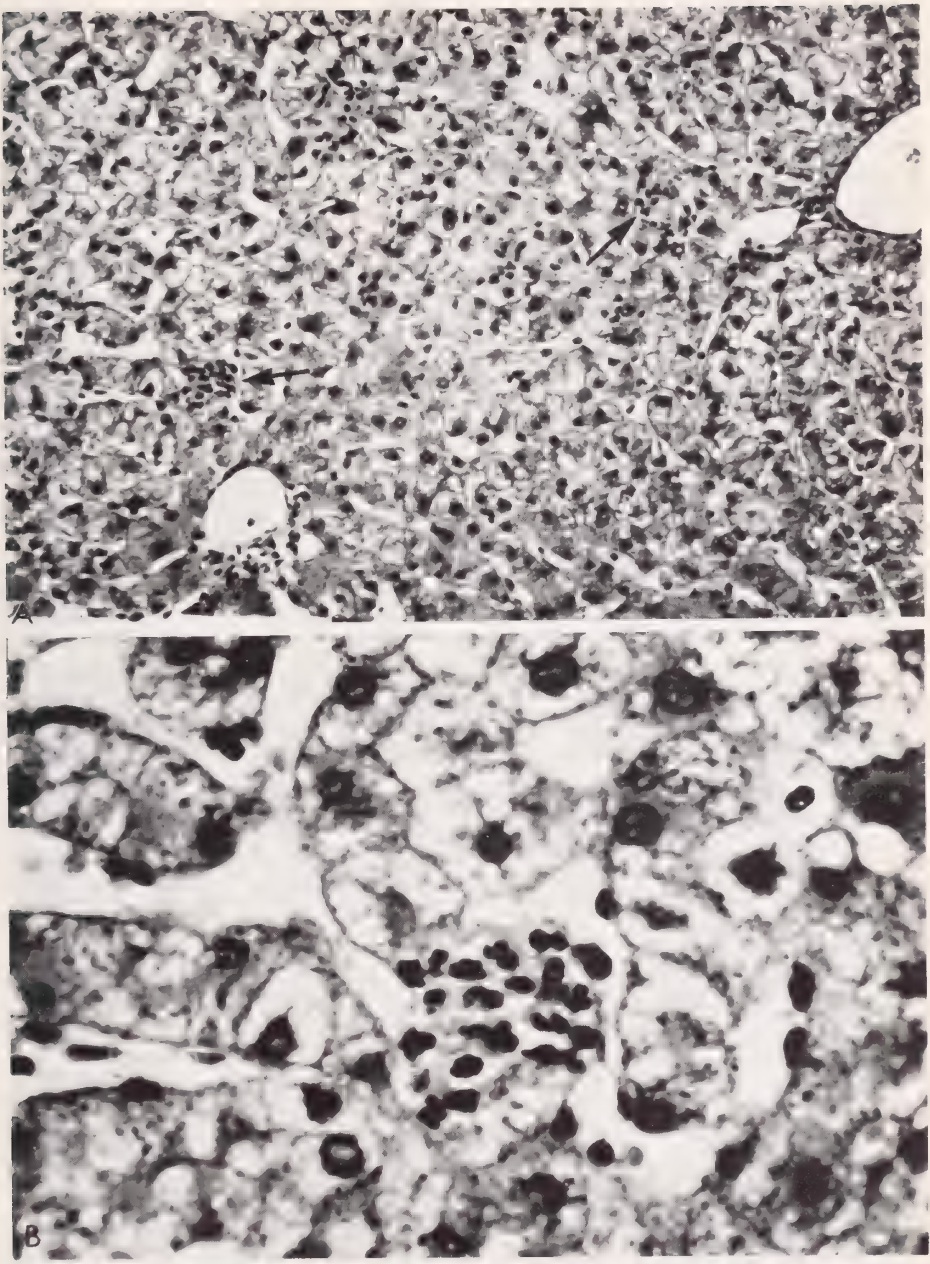

FIG. 1 A. Photomicrograph of liver biopsy. Necrosis of single hepatocytes with accumulation of polymorphonuclear leucocytes forms microabscesses (arrows). Occasional inflammatory cells are present in the sinusoids (Hematoxylin-Eosin, original × 40).
B. Microabscess (Hematoxylin-Eosin, original × 400).

also formalin-fixed, was similarly prepared. Micrographs were taken with a Hitachi HS-8 electron microscope. Liver obtained at autopsy, also formalin-fixed, was similarly prepared. Some hepatocytes were filled with round, uniform, electron-dense particles, approximately 20 mμ in diameter (Fig. 2). These particles were spherical, arranged in small clusters or rosettes, and

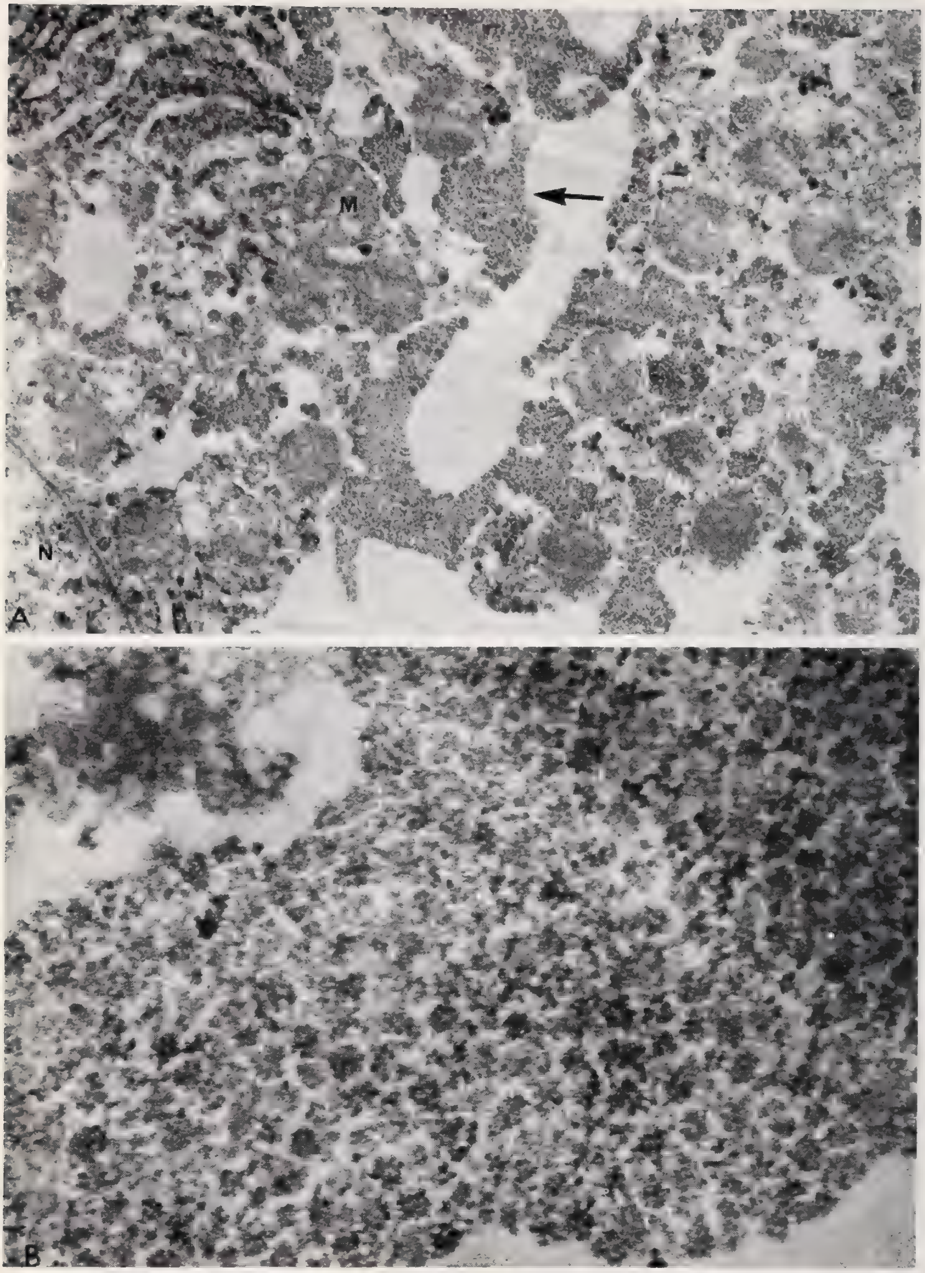

Fig. 2 A. Electron micrograph of liver biopsy. Sheets and small clusters of viral particles partially fill the cytoplasm and surround the nucleus (N), Golgi apparatus (G) and mitochondria (M). The closely approximated particles form rosettes (arrow) and are better preserved than the cellular organelles (Lead citrate, × 29,000).

B. Detail of a portion of a sheet of viral particles arranged in rosettes. The particles have well-defined peripheral membranes and denser central cores (Lead citrate, × 94,000).

formed distinct islets and sheets in the cytoplasm of the affected cells, mostly about the nucleus. The particles had well-defined peripheral membranes and denser central cores. Hepatic tissue obtained at autopsy was severely autolyzed and unsuitable for electron microscopic examination. Paraffin blocks of liver tissue from experimentally induced Coxsackie hepatitis were subjected to the same procedures as the human material, with deparaffinization and appropriate preparation for electron microscopy. These tissues were somewhat more autolyzed than the biopsy material from our case. However, similar distinct bodies, of 20 mμ diameter, were recognizable in some cells.

Discussion

Microabscesses were present in the liver of the newborn studied by Sussman, Strauss, and Hodes (2). Myocarditis was the major problem in this case and Coxsackie B virus was isolated from feces. Hepatitis in association with Coxsackie infection has been well documented in infants and children (2, 9–14). Hepatic tenderness was demonstrable in a 28-year-old virology laboratory technician who had been working with Coxsackie B virus and who became ill (3). Coxsackie B virus was isolated from cultures of his stool. Liver biopsy was not performed in this patient nor in the 21-year-old pregnant woman with hepatitis and Coxsackie B virus in the stool, studied by O'Shaughnessey and Buechner (4). Sun and Smith, however, demonstrated portal and parenchymal inflammation, and swelling of mid-zonal hepatocytes in a 19-year-old woman in whom acute hepatitis was a major manisfestation of infection with Coxsackie B, type 3 (5). The histologic changes of the postmortem liver of the present case are similar to those they demonstrated in biopsy. Embil, van Rooyen, and Nagler recovered Coxsackie A10 virus from the stools of 45 contacts during an outbreak of infectious hepatitis, as well as from the blood of 4 others (6). They were reluctant, however, directly to relate Coxsackie virus to the clinical hepatitis. Siegel and coworkers documented variants of the usual course of illness in Coxsackie infection (15). Their clinical and epidemiologic study of 43 patients included 15 in whom hepatomegaly, usually with tenderness, was prominent. By contrast, hepatitis was clinically documented in only 1 of 900 cases studied during a Coxsackie virus epidemic in the United Kingdom in 1965 (16).

The ultrastructural characteristics of the Coxsackie virus in tissue have been reported by Rabin and colleagues (17). They studied cardiac changes in experimentally induced Coxsackie B3 infection of mice and demonstrated Coxsackie virus antigen and viral particles within the cytoplasm of the cardiac myocyte. The particles in the cytoplasm of the hepatocytes in the biopsy of the present case appear identical to those they observed.

Coxsackie virus infections in the adult are usually self-limiting although recovery does not always occur (18). Although most unusual, hepatitis may complicate a Coxsackie virus infection and may prove fatal. Nonspecific inflammation of the liver without necrosis may be the earliest morphologic evidence. Necrosis of individual hepatocytes may follow with accumulations of polymorphonuclear leucocytes as microabscesses. Although clinical evidence of liver disease may be lacking, viral particles may be identifiable at this stage when, as in the present case, antibody titer is high. A more diffuse hepatitis with chronic inflammatory cells follows. The hepatitis may persist although the virus may no longer be demonstrable.

Acknowledgments

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Ileocolic Intussusception Presenting as a Left Upper Quadrant Mass, Masquerading as Pancreatic Pseudocyst

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Intussusception, the invagination of a proximal segment of the intestine into an adjacent distal segment is a well-known, rather commonly occurring cause of intestinal obstruction in infants and children. This condition and the subsequent intestinal obstruction are also seen in adults. Their occurrence in this segment of the population, however, is uncommon, accounting for only 5% of all intussusception (1). As noted by Roper (2), the condition is usually secondary to an intrinsic tumor and is not a clearcut clinical entity in the adult. This report describes intussusception occurring in an unusual and intriguing clinical setting.

Case Report

A 44-year-old male alcoholic was seen at the Bronx Veterans Administration Hospital complaining of severe, crampy abdominal pain, intermittent nausea, vomiting, and abdominal fullness for approximately one week prior to admission. He localized the pain to the left upper abdomen, with occassional radiation to the back and minimal relief on assuming a crouched position. He reported a weight loss of 30 lbs over a period of one month. Nine years prior, an investigation for gallbladder disease was unrevealing. On examination, he was noted to be cachetic and appeared chronically ill. The temperature was 98°F and pulse rate 82 per minute. The abdomen was flat and soft, bowel sounds were normal, and there was no evidence of previous surgery. There was an ill-defined, tender left upper quadrant mass which extended into the epigastrium. Rectal examination revealed a small amount of watery, brownish-colored stool which was negative for occult blood. The CBC was normal and the serum amylase reported at 33 dye units (normal: 45 200). Plain x-rays of the abdomen revealed a large mass forming a smoothly contoured indentation on the greater curvature aspect of the stomach. Scattered pancreatic calcifications were also noted (Fig. 1). An upper gastrointestinal contrast study demonstrated a large retrogastric mass consistent with pancreatic pseudocyst (Fig. 2). With these findings and in view of the patient's severe pain and discomfort, further investigation was deemed unwarranted and he was scheduled for surgical drainage of the presumed pseudocyst. However, on the day prior to surgery, he was noted to have a markedly distended and tympanitic abdomen with hypoactive bowel sounds. Rectal examination revealed a small amount of dark brown stool which was minimally positive for occult blood. Plain x-rays of the abdomen were obtained and revealed retained contrast material, from the upper gastrointestinal series, in the terminal ileum and proximal intestinal obstruction (Figs. 3A and B). The x-rays were reported as indicating intestinal obstruction secondary to retained barium. Sigmoidoscopy, performed following passage of a Cantor tube, revealed no pathology. The small intestine is an unusual area for barium inspissation; nonetheless, this was thought to be the site of obstruction. Exploration was indicated and the patient was operated on for pancreatic pseudocyst complicated by intestinal obstruction. At

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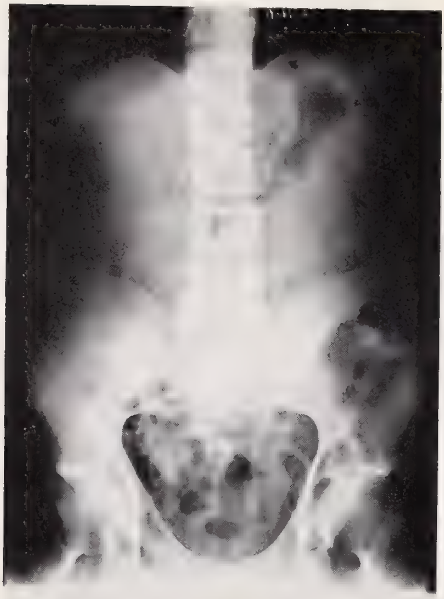

FIG. 1. Plain x-ray of abdomen showing deformed gastric shadow and numerous pancreatic calcifications.

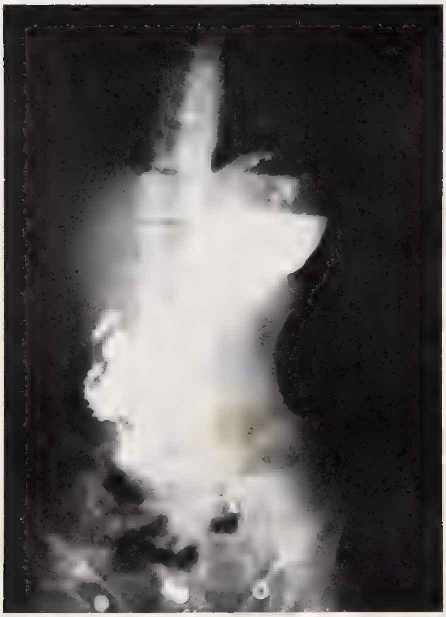

FIG. 2. Film from UGI series demonstrating retrogastric mass effect.

laparotomy, he was found to have a large left upper quadrant mass secondary to an ileocolic intussusception and incomplete rotation of the colon (Fig. 4). The right lower quadrant was empty of intestine. Following reduction, the cecum was noted to be quite mobile and unattached, and a mucocele of the appendix was found to be the cause of intussusception (Fig. 5). There was minimal chronic pancreatitis. The postoperative period was complicated by a bilateral labor pneumonia and a questionable coronary occlusion; but the patient recovered fully and was discharged three weeks after surgery.

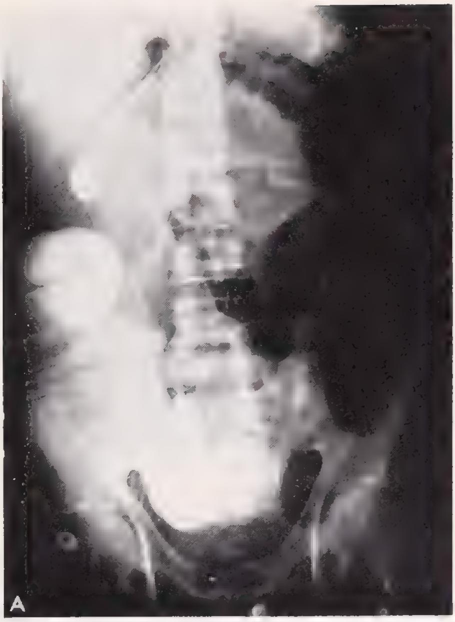

FIG. 3A. Retained barium in terminal ileum and multiple loops of gas-filled small bowel.

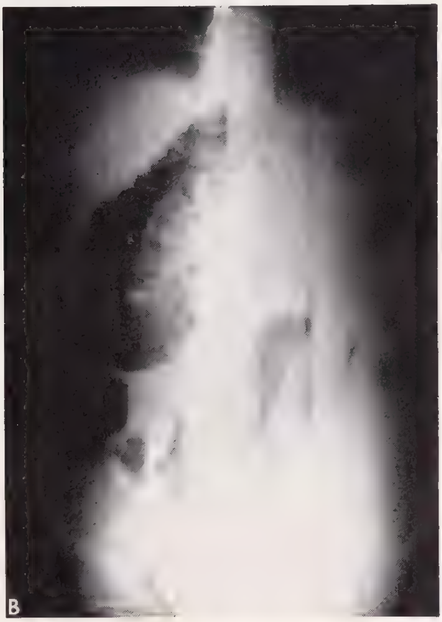

FIG. 3B. Right lateral decubitus film showing multiple air-fluid levels and, in retrospect, the gas-filled intestine of the intussusception.

Discussion

Intussusception in the adult (1) is a relatively uncommon disorder with diverse clinical manifestations (2) for which reason the diagnosis is often missed. Dean, Ellis and Sauer (1), reporting 96 cases of intussusception in adults, were able to demonstrate organic lesions in 84 cases. Of these 84 lesions, 58 were

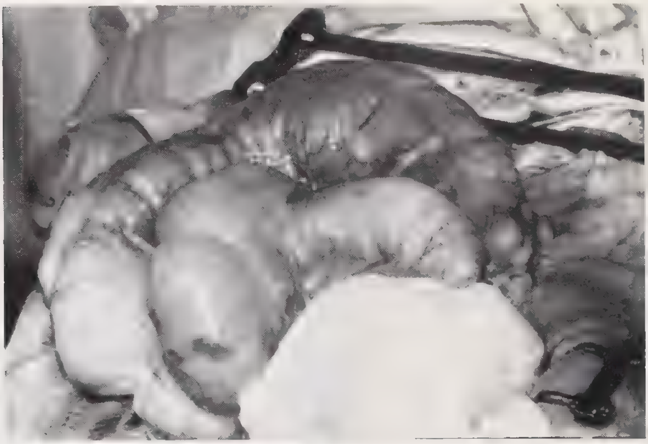

FIG. 4. Reduced intussusception and massively distended appendix.

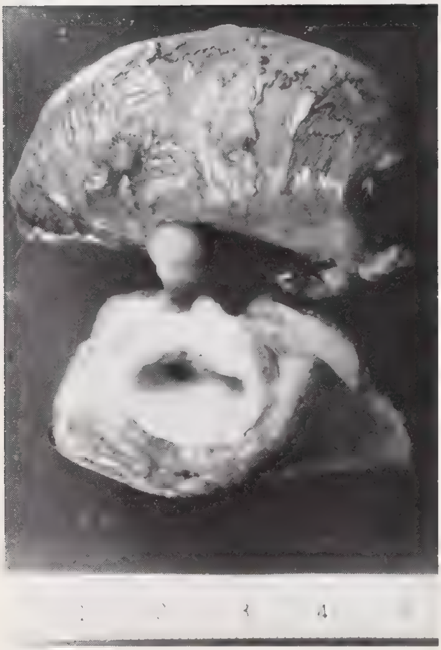

FIG. 5. Section of appendix illustrating the mucocele.

malignant. Lesions demonstrated were carcinomas, sarcomas, leiomyomas, lipomas, polyps, myxomata, heteroptic gastric mucosa, and Meckel's diverticuli.

In our patient, mucocele of the appendix was the etiologic factor, but his symptoms could not be attributed to this condition. Certainly, the history, physical examination and work-up made pancreatic pseudocyst or neoplasm a likely diagnosis. However, appearance of intestinal obstruction and hematest-positive material on rectal examination occasioned suspicion of erroneous diagnosis. Certainly, a more sophisticated interpretation of the x-ray film done at that time is compatible with intussusception. The sudden change in clinical course fortunately prompted exploration.

Reduction of the intussusception was accomplished. There being no necrosis of bowel, resection was unnecessary. The inciting agent, mucocele of the appendix, was resected.

Summary

A case of intussusception in an adult, with unusual coexistent clinical circumstances, has been presented. Though well documented as a cause of intestinal obstruction, this condition is not a common finding in adults and hence the diagnosis is not made initially. The appearance of intestinal obstruction prompted exploration. The case illustrates an instance of bowel filled with air and obstruction by intussusception, masquerading as pancreatic pseudocyst.

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Endometrial Carcinoma in Turner's Syndrome following Prolonged Treatment with Diethylstilbestrol

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Abstract

A 27-year-old woman with karyotype-proven Turner's syndrome who received approximately 15 gms diethylstilbestrol over an eight-year period for treatment of recurrent bleeding from congenital phlebectasia of the bowel and developed endometrial carcinoma is reported. Seven previously reported cases of Turner's syndrome who developed endometrial carcinoma after treatment with large doses of diethylstilbestrol are reviewed. Several unusual features in this group strongly suggest a causal relationship between diethylstilbestrol and the development of endometrial carcinoma and Turner's syndrome. The advisability of using estrogenic substances other than diethylstilbestrol for feminizing and maintaining feminization of patients with Turner's syndrome is discussed.

It has been suggested that long-term treatment with unopposed estrogens may be causally related to the development of endometrial carcinoma (1). Recent reports have cited seven patients with gonadal dysgenesis who developed endometrial carcinoma while on prolonged treatment with stilbestrol (2, 3).

This paper describes a patient with Turner's syndrome who developed endometrial carcinoma after being treated with a total dose of approximately 15 grams of diethylstilbestrol over an eight-year period. The drug was used in an attempt to prevent recurrent bleeding from congenital vascular lesions of the gastrointestinal tract as well as to develop secondary sex characteristics.

Case Report

A 27-year-old woman with karyotype-proven XO Turner's syndrome associated with laparotomy-proven vascular gastrointestinal anomalies entered Mount Sinai Hospital on November 6, 1972 because of menometrorrhagia of five months' duration. The diagnosis of Turner's syndrome with bleeding from vermiform phlebectasia of the bowel had been established on her first Mount Sinai Hospital admission in July 1965, at which time exploratory laparotomy and removal of gonadal streaks was performed (4). Postoperatively, she was started on diethylstilbestrol, 1 mg daily cyclically. No progestational drug was added. On this dosage she developed normal female secondary sex characteristics and had regular cyclic vaginal bleeding 3 to 4 days after diethylstilbestrol withdrawal.

In November of 1966 she was readmitted to Mount Sinai Hospital because of recurrent gastrointestinal bleeding. At that time her hemoglobin was 5.5 g/100 ml. After treatment with transfusions she was discharged on diethylstilbestrol 2 mg daily. In February of 1967 the dose of

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diethylstilbestrol was increased to 5 mg b.i.d. in an attempt to prevent further episodes of bleeding from her gastrointestinal vascular anomalies. She continued to have cyclic withdrawal bleeding with occasional episodes of menorrhagia. No further gastrointestinal bleeding occurred.

In April 1972 pelvic examination showed no palpable gynecologic pathology. Papanicolaou smear was reported as Class I. In July of the same year the patient began having more frequent menorrhagia which developed into menometrorrhagia.

In November of 1972 the patient complained of continuing menometrorrhagia and weakness. Pelvic examination at that time revealed a pelvic mass approximately 5 cm in diameter protruding through a dilated cervical os. The mass was on a thick stalk and was friable. The uterus was enlarged to 8–10 weeks gestational size. Hemoglobin at that time was 8.0 g/100 ml.

On admission to the hospital physical examination revealed a pale white female in no acute distress. Vital signs were normal. The neck was short with no definite pterygium. The breasts were well developed with darkly pigmented nipples. No breast masses were palpable. Normal pubic and axillary hair was present. There was no palpable lymphadenopathy. The chest was clear, the heart was not enlarged and no murmurs were heard. The abdomen was soft and nontender. There was a well-healed midline surgical scar from the umbilicus to the pubis. No liver, spleen, or kidney enlargement was palpable. The uterus was not palpable abdominally. Pelvic examination was as previously noted. There was no peripheral edema.

On November 7, 1972 polypectomy with dilatation and curettage was performed. The uterus was enlarged to 10 weeks gestational size and sounded to 10 cm with an irregular cavity. Pathology showed endometrial carcinoma with areas of pseudosarcomatous changes and psammoma bodies (Fig. 1). Benign hyperplastic areas were also present. Intravenous pyelogram, bone survey, barium enema, and liver scan were normal. Karyotype of the biopsy specimen showed 45 XO chromosomal constitution in 25 of 30 metaphases. The other 5 cells contained 44 chromosomes or less, consistent with broken cells or hypodiploid complement. The cancer was staged as an anaplastic IB and preoperative radiotherapy was recommended.

The patient was discharged from the hospital and underwent a course of radiotherapy as an outpatient, consisting of a tumor dose of 4,000 rads in 20 fractions over 31 days between November 27, 1972 and December 27, 1972, given via opposing anterior-posterior portals to the pelvis, measuring 15 x 15 cm with a 6 MEV linear accelerator.

She was readmitted to Mount Sinai Hospital on February 5, 1973 and on the following day underwent a total abdominal hysterectomy. At laparotomy the uterus was enlarged to the size of 6 weeks' gestation and there was evidence of the previous surgery for the removal of the ovarian streaks. There was no palpable lymphadenopathy and the liver was free of metastatic involvement by palpation. There was no gross evidence of extension of the tumor outside the uterine cavity. Exploration of the large and small bowel revealed a vascular pattern similar to that noted on her previous exploration (Fig. 2). Pathologic examination of the surgical specimen showed no evidence of viable tumor. The postoperative course was uneventful and the patient was discharged without estrogen therapy.

Discussion

Thus far, seven cases of endometrial carcinoma have been reported in patients with Turner's syndrome who have received diethylstilbestrol. One of these cases was also being treated for phlebectasia of the bowel (5). The amount of diethylstilbestrol received by these patients ranged from 2.8 to 9.0 grams over periods of 4 to 20 years.

The patient presented in this paper received a total of approximately 15 grams of diethylstilbestrol over a seven-year period both to prevent bleeding from her gastrointestinal vascular anomaly and to produce secondary sex characteristics. Large doses of estrogen were used because no other treatment for this type of lesion had been established. Though gastrointestinal bleeding

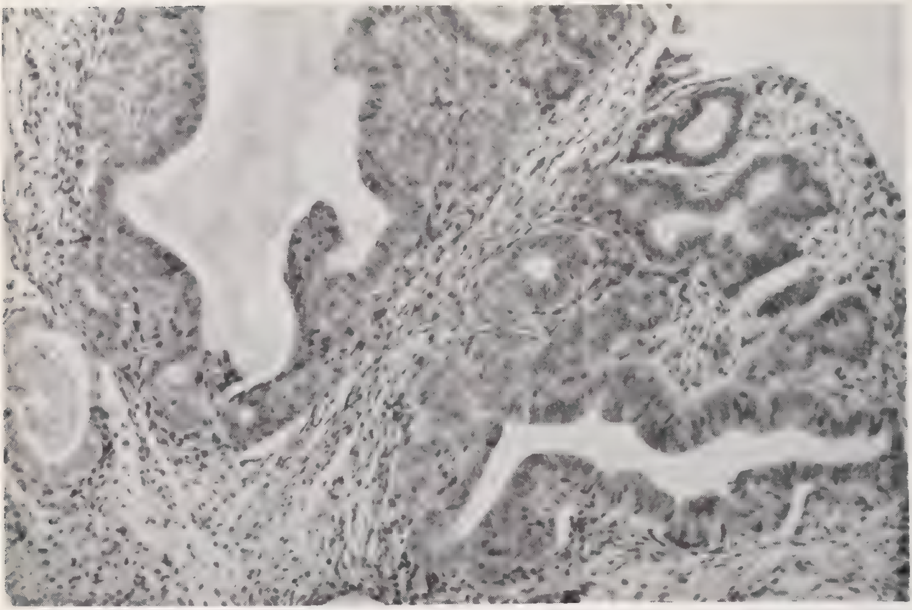

FIG. 1. Photomicrograph showing endometrial carcinoma with areas of pseudosarcomatous changes and psammoma bodies. (Hematoxylin and eosin; magnification, ×250.)

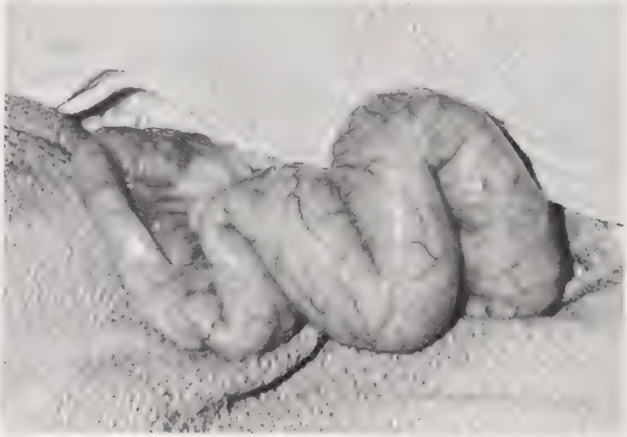

FIG. 2. Bowel lesion showing dilated serosal veins, telangiectasia and hemangiomata.

did not occur during the course of treatment, gross examination at surgery after this treatment showed no noticeable change in the vascular pattern of the bowel.

Patients with dysgenetic gonads have a high risk of developing neoplasms arising from their gonadal streaks. The incidence may be as high as 20 percent (6). Though the most commonly occurring tumor is the dysgerminoma, other tumors, including gonadoblastomas, interstitiomas, and Brenner tumors, have been reported. In addition, it has been shown that patients with Turner's syndrome have an increased risk of developing nongonadal tumors, especially those of neurogenic origin (7).

Diethylstilbestrol has been shown to cause adenocarcinoma of the endometrium in experimental animals (8). Female offspring of patients treated with diethylstilbestrol during the first trimester of pregnancy have developed adenocarcinoma of the vagina (9). One could, therefore, postulate that in patients with Turner's syndrome, who may have a genetically determined propensity for developing neoplasms, the use of diethylstilbestrol might well magnify the potential risk of carcinogenesis in the uterus.

Review of the seven previously reported cases and the present case shows three important characteristics about this group of patients which strongly suggest that the administration of large doses of diethylstilbestrol played a causal role in the development of uterine carcinoma. First, the age of the patients reported ranged from 26 to 32 years. The average age at the time of diagnosis of endometrial carcinoma in the genetically normal population is 55 years. Secondly, the pathology of the tumors in the cases under discussion was not that usually seen in uterine carcinoma but rather an uncommon variety of adenomatous and epithelial elements. Finally, there is only one reported case of a spontaneously occurring adenocarcinoma of the uterus in a patient with Turner's syndrome (10).

All of the reported patients with Turner's syndrome who have developed endometrial carcinoma after prolonged administration of estrogens have been treated with diethylstilbestrol. Though there is no specific evidence that the use of another type of estrogenic agent would prove to be less carcinogenic after prolonged administration in patients with Turner's syndrome, the information currently available suggests the advisability of using estrogenic agents other than diethylstilbestrol in the long-range management of this group of patients. It might also be of value to add a progestin to the regimen.

All patients with Turner's syndrome on long-term estrogen replacement therapy must be closely supervised. Frequent gynecologic examinations and cytologic smears should be performed. The appearance of irregular or unusually heavy menstrual bleeding should be thoroughly investigated with uterine biopsy or curettage. Hopefully, more extensive study of the use of estrogenic substances in patients with Turner's syndrome will lead to a better understanding of the interaction between estrogens and genetically abnormal cells and to a clarification of the optimal means of feminizing and maintaining feminization of the patient with gonadal dysgenesis.

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Studies on Melanocytes III. Melanocytes in Muscles of Mastication

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Abstract

Giant melanocytes were observed in the masseter and temporalis muscles of all human fetuses and neonates examined, both Caucasian and Negro. These cells are invariably absent in adults of both races. A finding exactly opposite to that of the nasal mucosa where melanocytes are present in adulthood but uniformly lacking in fetal and neonatal material. In keeping with these observations, numerous primary melanomas of the nasal mucosa are documented but there is no case recorded of this tumor arising in the muscles of mastication.

The extra-epidermal distribution of melanocytes in vertebrates has been reviewed.

Introduction

While the occurrence of melanocytes in such extra-epidermal sites as cutis, mucous membranes, leptomeninges, eye, and inner ear is well recognized, their presence within human striated muscle has not been recorded to our knowledge. It is the purpose of this presentation to report the regular occurrence of melanocytes in the muscles of mastication of man.

Materials and Methods

A formalin-fixed and decalcified cranium of a full-term human neonate was embedded in nitrocellulose (celloidin) and sectioned serially in a frontal plane (25 micra thick sections). These sections were stained with hematoxylin and eosin. In order to extend this study, material from 6 fetuses, 12 to 18 weeks gestational age, was examined. Here paraffin sections were used and a special stain for melanin (Fontana-Masson). Samples of masseter and temporalis muscles were removed at autopsy from 9 neonates, 12 adults ranging from 27 to 81 years of both races and from a 5-year-old black girl. The autopsy material was stained with a modified Warthin-Starry technique which is more specific for melanin and does not stain the age-dependent lipofuscin of striated muscle.

Results

Numerous elongated and deeply pigmented large cells containing a finely granular brown material were seen within the masseter and temporalis muscles bilaterally. These cells were located between muscle bundles or followed small blood vessels within the substance of the muscle (Figs. 1, 2).

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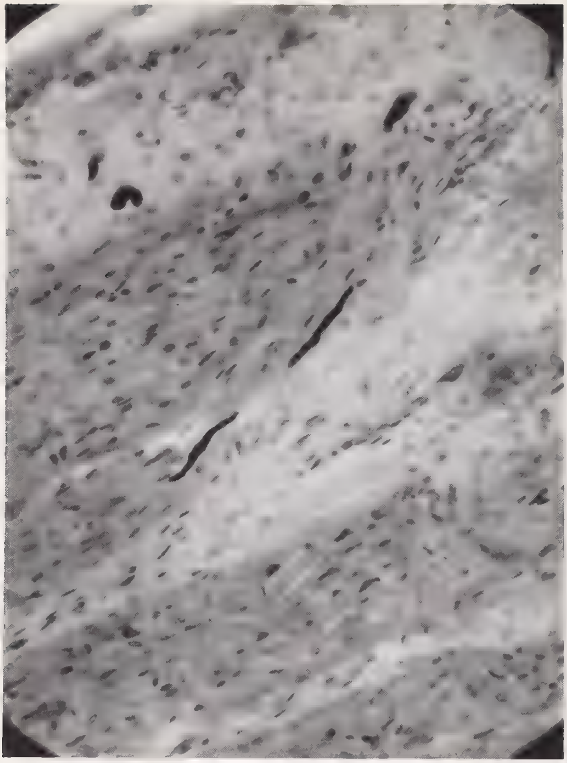

FIG. 1. Five melanocytes are in this field. The 2 central ones are in focus (Hematoxylin & Eosin 400x).

Melanocytes were readily found in the fetal and neonatal material as well as in the tissue from the 5-year-old. They are uniformly absent in the adult specimens. We have no samples from older children or adolescents. Specimens from a 27-year-old Negro man are negative. It is possible that the age-related disappearance of melanocytes is connected with puberty. These findings are opposite to those of the nasal mucosa where melanocytes are present in adulthood but uniformly lacking in fetal and neonatal material. In keeping with these observations, numerous primary melanomas of the nasal mucosa are documented, but there is no case recorded of this tumor arising in muscles of mastication.

Discussion

The neuroectodermal origin of the pigment cells of vertebrates, especially those which produce melanin in the skin has been well established. Embryologic support comes from experimental studies, particularly in amphibians and birds, which have shown that neural crest extirpation results in a total absence of pigment cells, whereas grafts of neural fold produce pigment cells in embryos of the same or different species. Explanted neural fold has also been shown to produce pigment cells in vitro (1). In a study of silver-impregnated

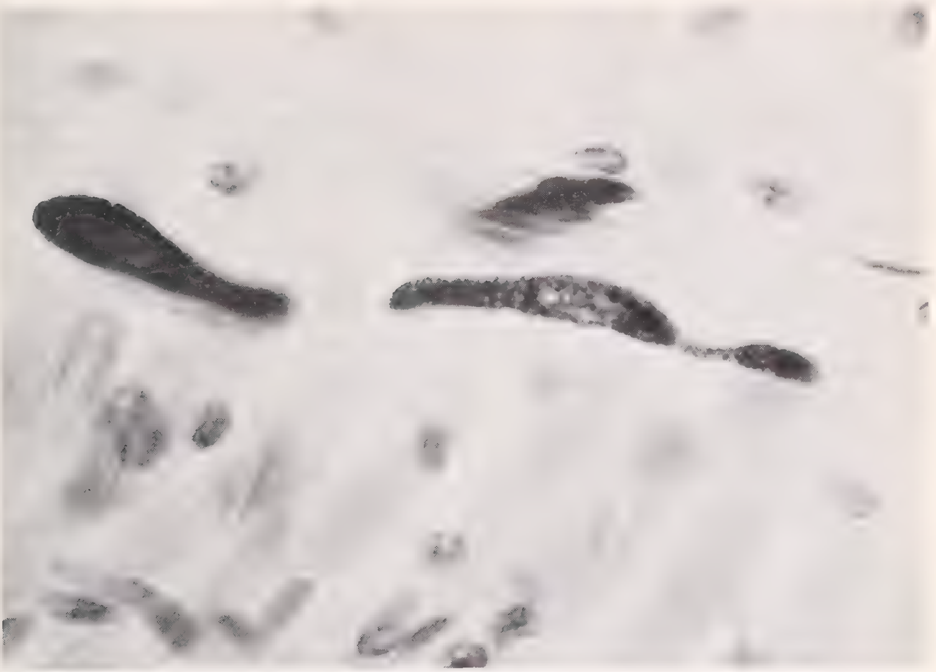

FIG. 2. Oil immersion brings out the cytoplasmic granules and the vesicular nucleus. Skeletal muscle fibers in lower half (Hematoxylin & Eosin 1200x).

human embryos, Boyd (1) identified dendritic melanocytoblasts in the mesoderm and epidermis as early as the 40 mm crown-rump length stage. However, factors influencing the migration of these neuroectodermally derived cells remain obscure.

In addition to the epidermis and its derivatives (hair, feathers, nails) melanocytes occur in a variety of locations in vertebrates. Scattered melanocytes are present throughout the dermis. The blue nevus is produced by an accumulation of melanocytes. Similarly, the Mongolian spot represents a localized concentration of melanocytes in the dermis of the sacral area, whose pigment is elaborated in embryologic life long before it appears in the epidermis (2). The nevus of Ota (8) which involves the facial skin (usually on one side) and the ipsilateral conjunctiva, sclera, choroid, nasal and oral mucosa as well as the nevus of Ito, a related pigmentary disorder of the acromioclavicular and pectoral skin, are a result of melanocytes within the cutis.

Melanocytes also have an extensive distribution within mucous membranes. They have been identified in the mucosal lining of the oral cavity (3), the embryonal dental lamina (4), esophagus (5), nasal cavity (6), larynx (7), middle ear (8), vagina (9), and urethra (10) in man. They also occur in the glands associated with the mucous membranes of the mouth (11), upper respiratory tract (5, 6), and urogenital tract (bulbo-urethral glands of Cowper) (1).

The leptomeninges are another site at which melanocytes have commonly been described in man. Boyd (1) also reported these cells in the choroid plexus and cerebellum as well as in the pia in pigs.

With regard to the eye, intraocular pigment cells are well recognized in the choroid, iris, and retina. Markert and Silvers (12) also found melanocytes in the nictitating membrane and Harderian glands of the orbit in the mouse.

Melanocytes also occur within the viscera. Markert and Silvers (12) described them in the parathyroids and thymus of the mouse. Grant (13) reported melanocytes in the subepithelial connective tissue of the uterus and fallopian tubes, in the peritubular sheaths of the epididymis and the capsule of the adrenal glands in sheep. Masson (14) found these cells within the adrenal medulla and regional lymph nodes in man. Goldberg (15) observed melanosis of the subcutaneous, subperitoneal, subpleural and intermuscular connective tissue in calves. Boyd (1) occasionally observed argentaffin premelanocytes in the general mesenchyme and more commonly in the connective tissue of the orbit and in relation to the developing inner ear in human embryos.

In lower vertebrates extra-epidermal melanocytes extensively permeate the mesenchymal tissues and possible sites include nearly every organ. They are commonly present in the perivascular connective tissue along major blood vessels, in peripheral nerves and ganglia and within the walls of the coelomic cavity (16). Boyd (1) described melanocytes in the interstices of muscles and in the periosteum and perichondrium of lower forms. The Japanese Negro-fowl represents an extreme example of the widespread distribution of melanocytes wherein all the connective tissue and viscera (including the heart) contain these cells (2).

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Lateral Subcutaneous Internal Sphincterotomy for Anal Fissure

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Abstract

Minor complications following internal sphincterotomy for anal fissures are rather high, with an incidence of 28% to 50%. The lateral subcutaneous sphincterotomy offers very good results and the technique is simple.

The early results of this operation on 100 patients have confirmed the advantage of the new technique. Minor complications were minimal.

Internal sphincterotomy has for many years been regarded as the ideal method of curing anal fissures. However, the minor complications, such as stool soiling, are rather high, with an incidence of 28% to 50% (1–3). This prompted us to evaluate a new technique, lateral subcutaneous sphincterotomy, which has appeared to offer very good results (4–7).

Etiology

Numerous hypotheses have been propounded in regard to the etiology of the anal fissure: vascular, infectious traction of anal valve or papilla, diseased skin and smooth muscle, and trauma or mechanical theory (8–10). Each of these theories is correct in regard to some fissures. The majority of anal fissures occurs in the posterior midline or adjacent area, with an incidence of 99% in the male and 85% in the female (10). Why should the fissure be so prone to occur in the posterior median plane? It has been generally believed that the posterior lower edge of the anal canal is less well supported by the external sphincteric muscle. A Y-arrangement of superficial and subcutaneous external sphincteric muscle implies a lack of support of the anal canal epithelium posteriorly rather than elsewhere in the circumference (9, 10). It is true that the superficial compartment has the striking feature of a strong, tough, and triangular posterior extension to the coccyx. The supporting muscular fibers, however, are well developed in the posterior midline, as illustrated by our studies (Fig. 1) (11). Therefore, the lack-of-support theory is not, in itself, sufficient to explain the predilection of posterior occurrence. Other factors that play a role in the formation of anal fissures are an expansibility of posterior wall and the elliptical shape of the anus.

Expansibility of the Posterior Wall: Because the coccyx is relatively mobile, the posterior anal canal is much more expansile than the anterior wall. The anterior midline is firmly anchored to the ischiopubic bones along with the

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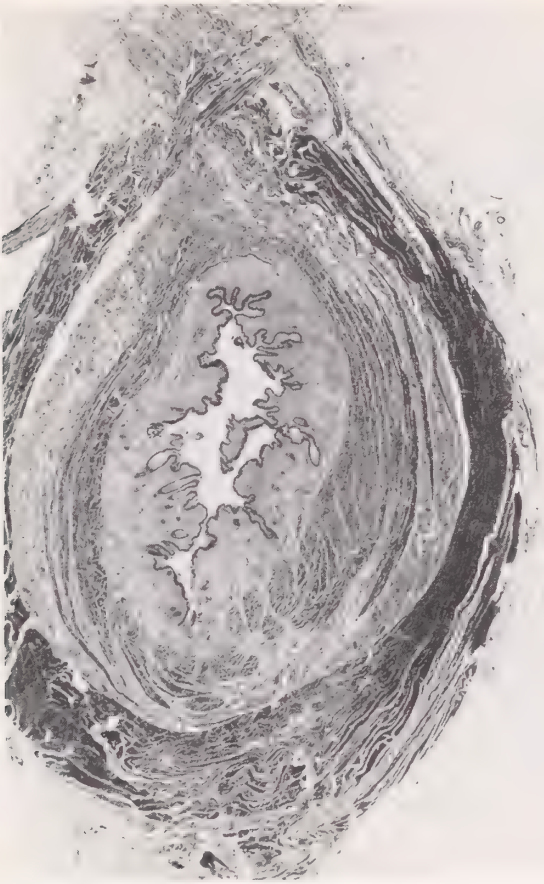

FIG. 1. Cross-section of the anus at the level of the superficial sphincter. The anterior portion of the external sphincter is decussated while the posterior portion of the external sphincter is circular.

perineal body in the male, while in the female it is loosely attached to the bony pelvis because of the vaginal canal's interposition between the rectum and pubis. In other words, the posterior anal canal is far more expansile than the anterior wall in both the male and female, though considerable expansibility is seen in the female anterior anal canal (12).

Elliptical Shape of the Anus: The anus is elliptical in shape when at rest, with a greater diameter in its anteroposterior direction (Fig. 1). It is well known that when the distal colon is obstructed, the cecum is the most vulnerable part to rupture because of its greater radius. By the same token, when a rubber glove is blown up, the palm is dilated far more than the digits; i.e., the tension of the wall is proportional to the radius (Leplace Law: T = P.R. [T: Tension, R: radius]). Therefore, during the passage of a large, hard stool mass, greater tension may be exerted on the posteroanterior direction than the lateral wall because of its greater radius. Since the posterior wall of the anus is more expansile than the anterior wall, when stretching exceeds the natural barrier of the anal skin, a tear may occur in the posterior wall.

Once the skin tear occurs, an infection may often supervene on the fissure and form a characteristic "red-colored sentinel pile." It is presumably due to chronic irritation of the lower edge of the ulcer from the exudate that causes lymphostasis and edema. The local irritation also causes spasm of the internal sphincteric muscle, and after several months the muscle fibers become fibrosed, which gives rise to permanent contracture (13). Painful defecation inhibits the act; hard stool forms in the rectum, which is even more traumatic when eventually passed. The patient discovers that a laxative gives relief; thus some take them for years and dare not give them up. As a result the stenosis of the anal canal becomes worse and it is difficult to evacuate the well-formed stool.

Materials and Methods

One hundred patients were subjected to lateral subcutaneous sphincterotomy: 48 males and 52 females ranging in age from 18 to 75, an average of 39. The majority of the group was between the age of 20 and 40. Sixty-seven patients had posterior fissures; 10 had both anterior and posterior fissures (five male, five female); anterior fissures were noted in 17 females and one male; five fissures were located in the lateral aspect of the anus in those who had previous rectal surgery. In addition to fissures, 15 patients had hemorrhoids, one with condyloma accuminata, seven with anal papilloma and five with anal fistula. The presenting symptoms were mainly pain and bleeding in 96 cases; four had only pain. The onset of disease ranged from three months to 20 years, with an average of two and one-half years.

The operation was performed with spinal or general anesthesia. No preoperative bowel prep was given because of pain. Under anesthesia, the anorectum was examined with a proctoscope or sigmoidoscope. One percent Xylocaine solution was infiltrated in order to create a submucosal plane. The needle was inserted at the intersphincteric groove of the left midlateral area and the solution injected into the submucosa to above the pectinate line. This was guided by the left index finger, which was inserted into the anal canal to avoid perforation of the anal mucosa. The internal sphincter was divided with a modified method of Notaras (4) and Millar (7). Following the small incision of the skin at the left lateral intersphincteric groove, a curved baby scissors was passed to separate mucosa from the internal sphincter above the pectinate line. A curved No. 12 blade was introduced along the plane of the scissors and the blade was turned 90°, facing the cutting edge outward toward the internal sphincter. The internal sphincter was then stabbed with the aid of the left index finger and the sphincteric muscle was divided as the knife was withdrawn. The wound was packed with iodoform gauze in order to eliminate hematoma and infection (Fig. 2). The packing was removed by the first or second postoperative day and the patient was discharged on the second to fourth day. Eighty-five cases were subjected to lateral sphincterotomy only, 10

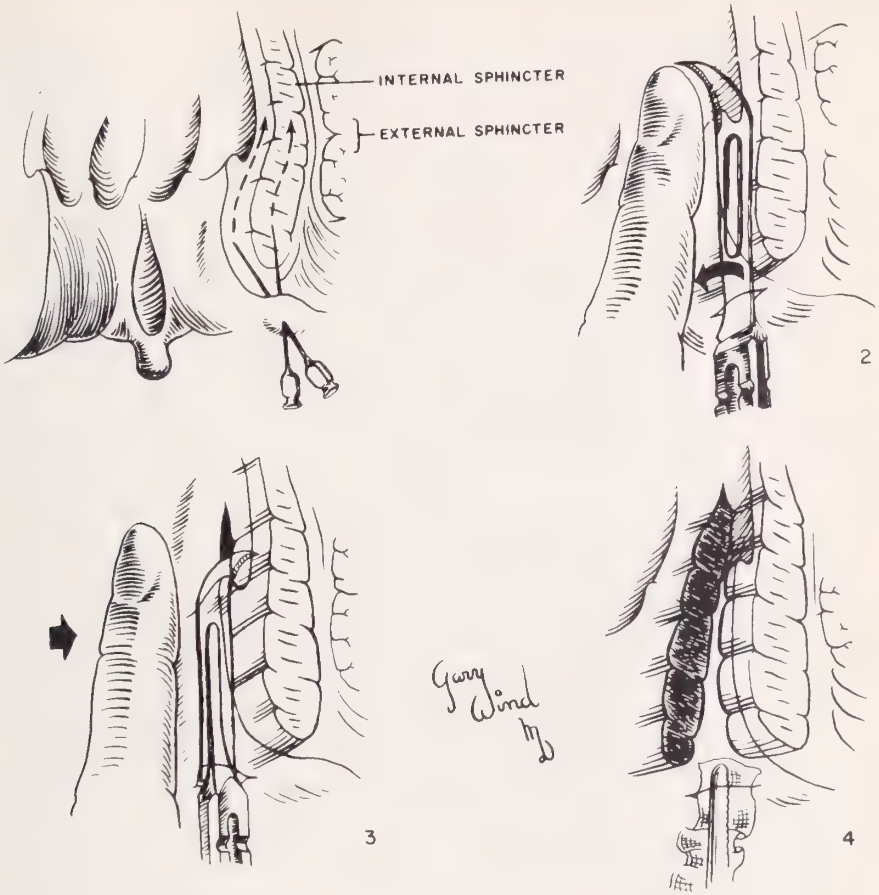

FIG. 2. Demonstration of lateral subcutaneous internal sphincterotomy :
1) Infiltration of epinephrine solution into submucosa and internal sphincter.
2) Insertion of knife and turn the blade toward the internal sphincter.
3) Dividing the internal sphincter as withdrawing the knife.
4) Complete the division and insert packing into wound.

with excision of the sentinel pile, seven with excision of anal papilloma, and five with fistulectomy in addition to sphincterotomy.

Results

Eighty-seven of the 100 patients were followed up to three years. Within six weeks all patients improved except for one who required hemorrhoidectomy six weeks after sphincterotomy for existing prolapsing hemorrhoids. Three became infected, but subsided with conservative treatment. Fecal soiling was noticed in six patients at preoperative examination and all of them improved with surgery, though three patients claimed occasional soiling when diarrhea occurred. Pain persisted in three patients, but to a far lesser degree than before operation. One patient had postoperative bleeding requiring ligature of bleeders. In another case, the ulcer failed to heal, but symptoms improved. Five patients noticed perineal ecchymosis without consequence; no anal stricture, incontinence, recurrence, or key-hole deformities were observed in this series.

Discussion

Sphincterotomy for the treatment of anal fissures was first applied by Goodsall (14). He divided the most prominent sphincter at the floor of the fissure, believing it to be the external anal sphincter, and this method has been practiced widely ever since. Eisenhammer (13), however, demonstrated clearly that this band of muscle was in fact the inferior margin of the internal sphincter. Following posterior internal sphincterotomy, the pain was relieved so dramatically that minor postoperative complications were often not mentioned by the patient and rarely called to the surgeon's attention. However, critical evaluation was carried out by a number of investigators and disclosed a high incidence of minor fecal soiling, ranging from 28% to 50% (1–3). It was thought that the relatively insensitive median cicatricial furrow in the dorsal wall of the anal canal, after posterior internal sphincterotomy, allowed fecal matter to escape or dribble from the rectum to the exterior without evoking the normal sphincter response (15). This disadvantage has been considerably minimized by avoiding the incision on the anal canal with lateral open sphincterotomy (16). Even more gratifying results were reported with the simpler technique of lateral subcutaneous sphincterotomy (4–7); the wound healed faster, without key-hole deformities and with little incidence of fecal soiling. The results were far superior to the standard posterior internal sphincterotomy in regard to complications. Furthermore, this procedure can be performed under local anesthesia, although we have used spinal or general anesthesia on our patients.

The early results confirmed in general the advantage of this new technique and most of the patients were gratified. Minor complications of hematoma and wound infection were seen in the early cases, but they were eliminated by the insertion of packing into the wound for one or two days postoperatively. We have found it easier to divide the internal sphincteric muscle with the curved No. 12 blade than the straight blade.

We are in full agreement with Hoffmann and Goligher (6), who have not hesitated to recommend this technique for the routine treatment of anal fissures.

Conclusion

1. A new and simpler technique, lateral subcutaneous sphincterotomy, was applied to 100 cases of chronic, intractable anal fissures and followed for three months to three years in 87 cases.

2. Etiology of idiopathic-primary anal fissures has been discussed.

3. The early results were very gratifying and confirmed the excellent results of others.

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RADIOLOGIC NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., COEDITORS

Case No. 386

Submitted by

ALEX BERENSTEIN, M.D.

A 62-year-old woman was admitted to The Mount Sinai Hospital because of severe right costovertebral angle pain, hematuria, fever, and a mass palpable anteriorly in the right midabdomen. An IVP performed one year previously had shown a staghorn calculus in the right renal pelvis at the level of L3-4 with preservation of function of the upper portion of the collecting system. (Figs. 1 and 2) A cholecystectomy had been performed in the interim.

An IVP was performed. On the preliminary film of the abdomen it was noted that the known right staghorn calculus had changed its location and was seen to be overlying the transverse process of L4 on the right where it was partially obscured (Fig. 3). After injection of opaque material, the right kidney entirely failed to function. Right posterior oblique projection from the IVP series demonstrated the displaced staghorn calculus near the lower pole of the kidney as well as a few tiny concretions more peripherally (Fig. 4). A soft tissue mass was also apparent in relation to the lower pole.

Efforts to pass a right ureteral catheter were unsuccessful; an obstruction was encountered at 25 cm. as measured from below by the urologist. With catheters in place, the patient was examined with image-intensified fluoroscopy. The catheters were seen to impinge on the staghorn calculus which completely blocked their retrograde passage (Fig. 5). An emergency nephrectomy was performed. Pyo-hydronephrosis was found with the staghorn calculus at the uretero-pelvic junction.

Discussion

The pertinent findings in this case included a mass palpable transabdominally in association with a displaced staghorn calculus in a nonfunctioning kidney. Differential diagnosis includes 1) hydronephrosis and pyo-hydronephrosis, 2) xanthogranulomatous pyelonephritis, 3) renal sinus lipomatosis or fibrolipomatosis with stone; and 4) neoplastic conditions, particularly squamous cell carcinoma associated with stone and chronic infection.

When infection is superimposed on calculous hydronephrosis, a pyo-hydronephrosis will result. The essential urographic findings in this condition

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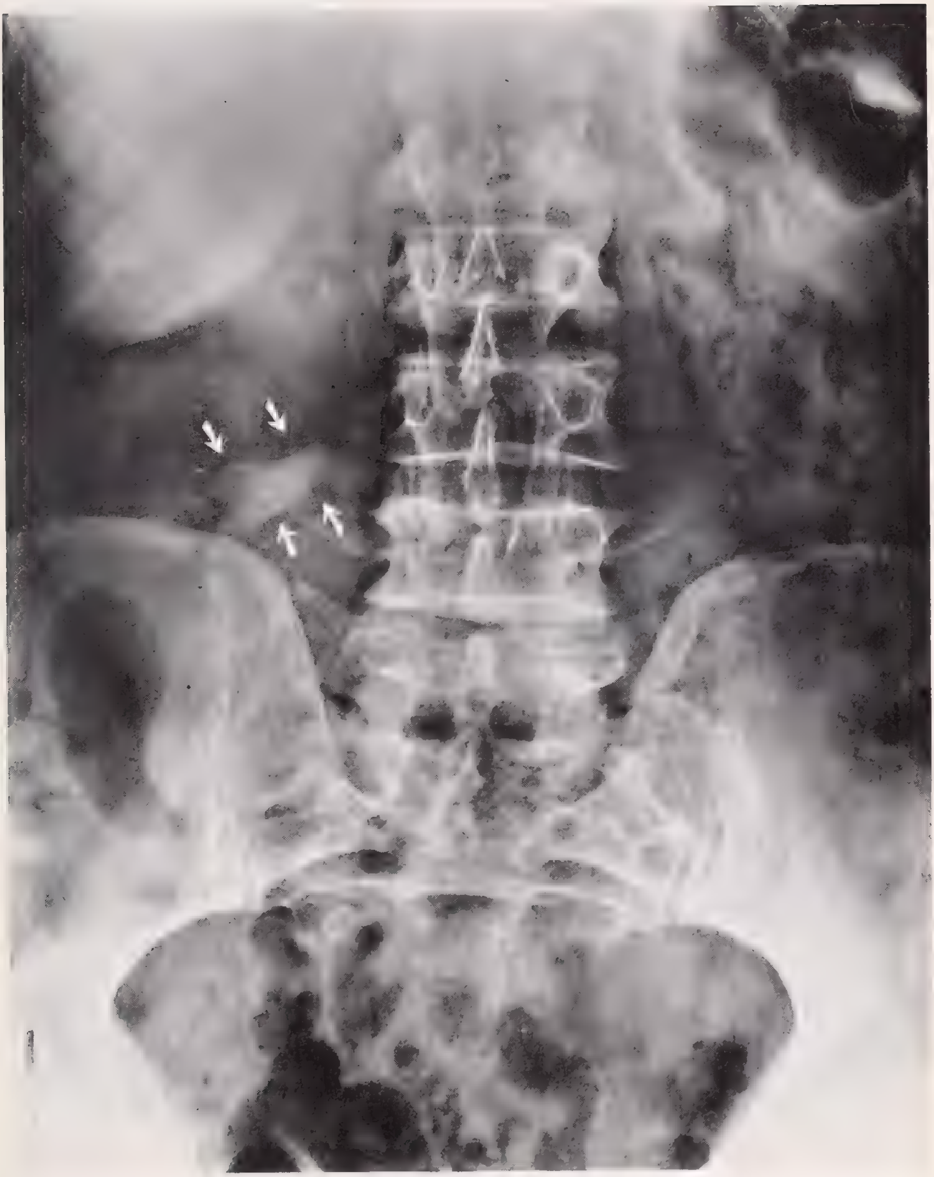
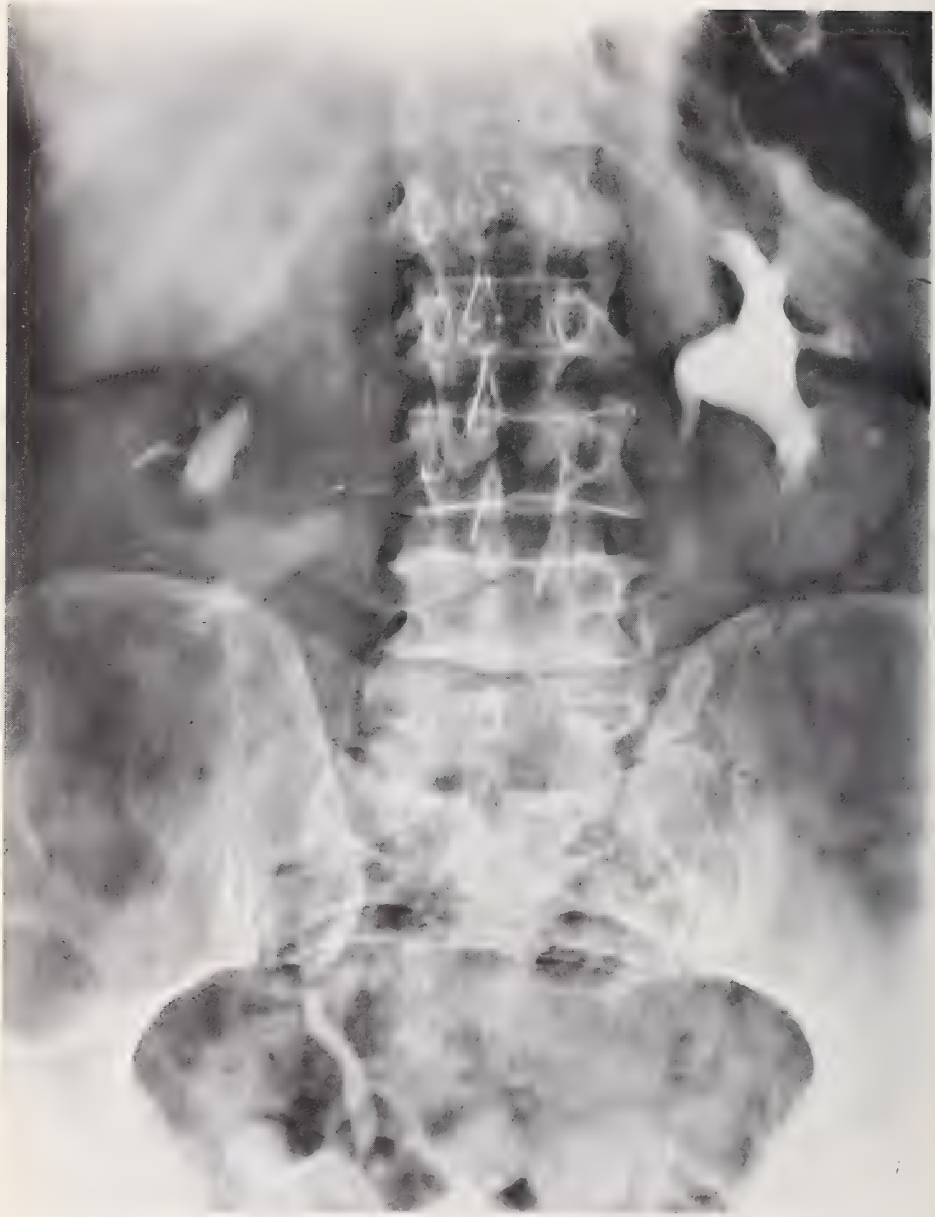
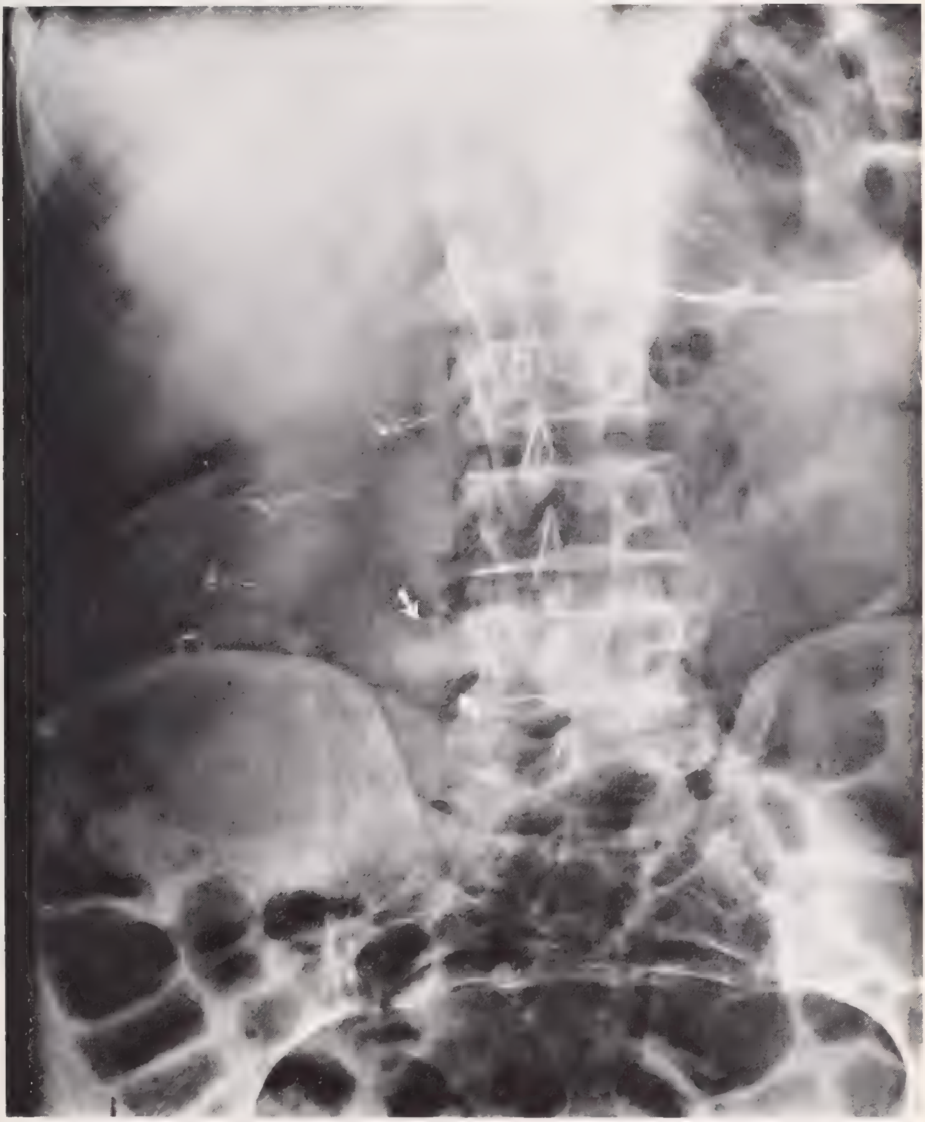


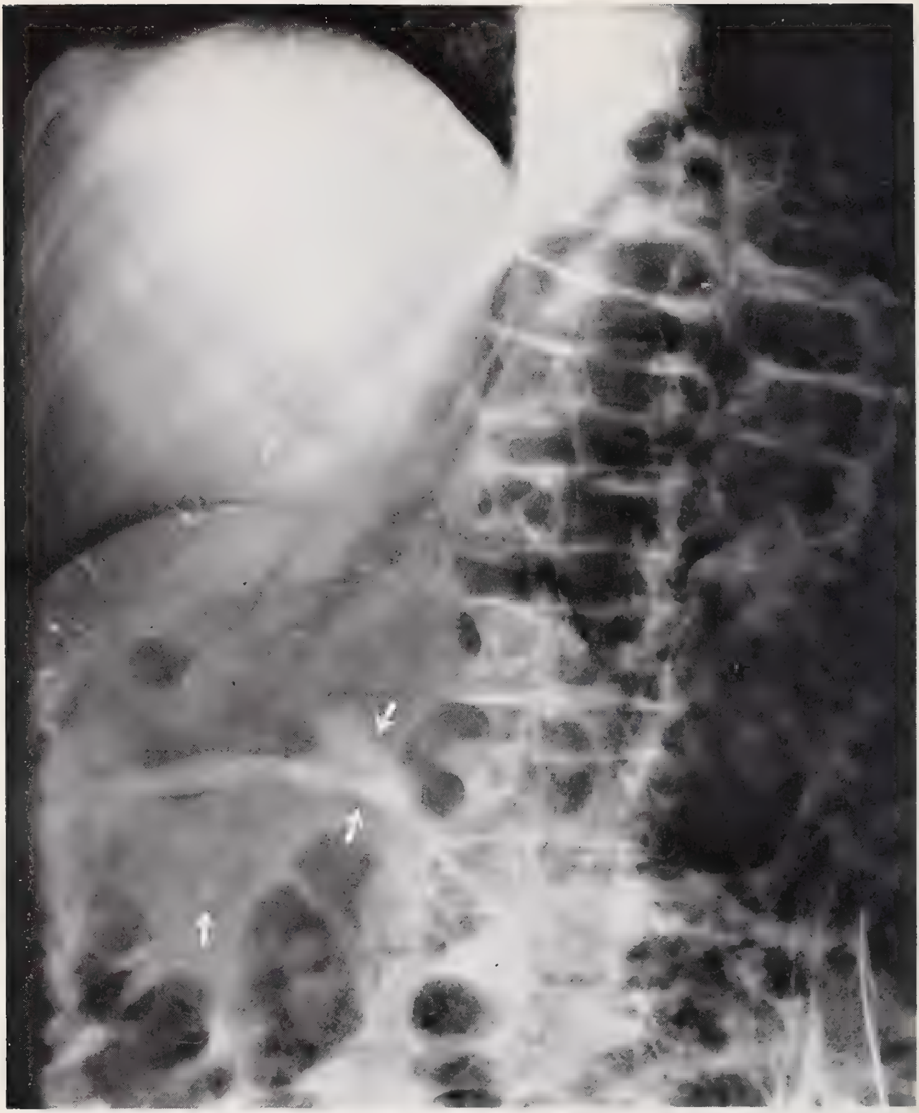
Case 386, Fig. 1. Plain film of the abdomen shows a staghorn calculus overlying the medial portion of the right kidney (between arrows).



Case 386, Fig. 2. Ten-minute film from intravenous pyelogram shows opacification of the upper portion of the right internal collecting system with excreted opaque material plus very minimal additional opacification of the lower portion of the internal collecting system and pelvis where the staghorn calculus is located. The left kidney is normal.

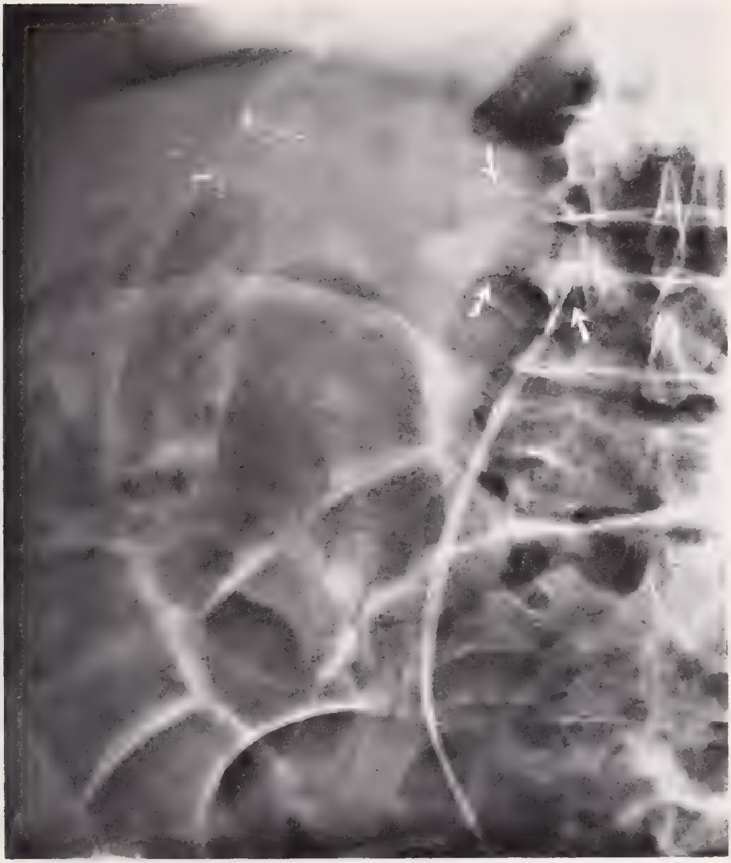


Case 386, Fig. 3. Preliminary film of the abdomen shows a change in location of the previously described staghorn calculus; it has been displaced medially and now overlies the transverse process of L4 (between arrows).



Case 386, Fig. 4. Right posterior oblique projection throws the staghorn clear of the spine (between arrows) and clearly demonstrates its reorientation. (Compare with Fig. 1.) A few tiny densities are seen more peripherally (arrow). There is increased soft tissue density in relation to the lower pole of the kidney (difficult to appreciate in this reproduction).

include the presence of single or multiple calculi plus poor or absent excretory function. Evidence of fixation or limited mobility of the involved kidney has been stressed as an important and not infrequent finding. Renal mobility can be demonstrated radiographically by comparing films exposed at the extremes



Case 386, Fig. 5. The staghorn calculus is noted (between arrows) and the tips of the ureteral catheters are in relation to its most medial portion (arrow).

of inspiration and expiration, or alternatively, in supine and erect positions. The normal kidney should have an excursion of approximately the height of one lumbar vertebral body. Other indications of infection include haziness of the renal outline, poor visualization or complete obliteration of the outline of the psoas muscle, and lumbar scoliosis with concavity towards the affected side. An associated inflammatory mass may be present and resultant displacement of the kidney may be another important diagnostic sign. The nature and direction of the renal displacement may indicate the location of the inflammatory mass, whether cortical or perinephric in nature. In the case presented, an associated perinephric inflammatory mass produced medial displacement of the kidney along with displacement and reorientation of a staghorn calculus.

Case Report: DISPLACEMENT AND REORIENTATION OF A STAGHORN CALCULUS.

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Case No. 387

Submitted by

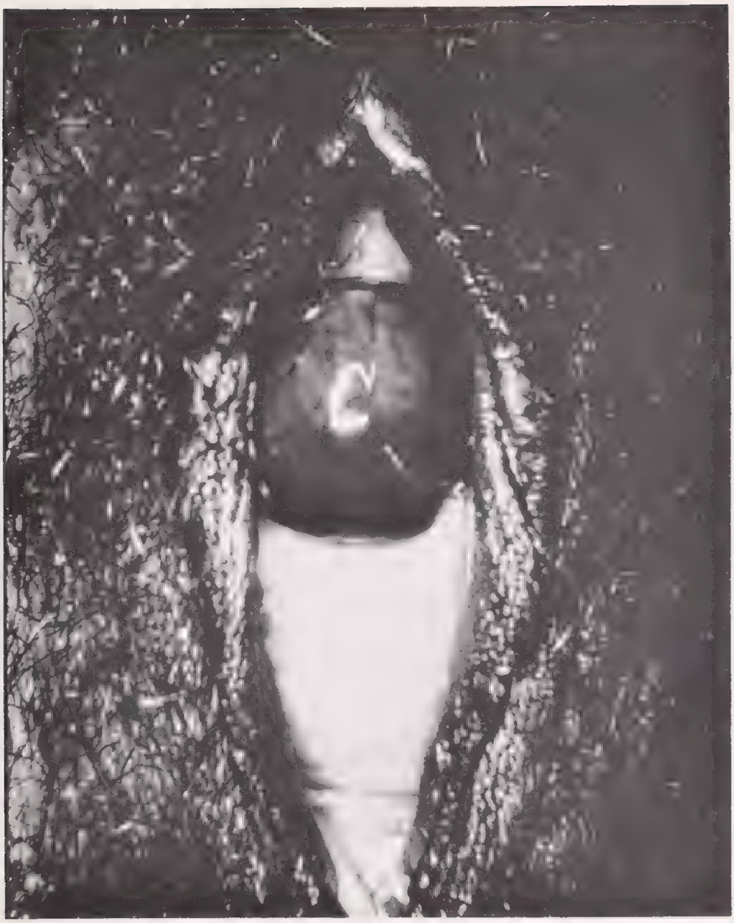
ALEX BERENSTEIN, M.D.

A 33-year-old woman came to the Emergency Room because of a prolapsing urethral mass first noted four months previously, associated with intermittent hematuria, dysuria, and frequency of urination. One day prior to admission the prolapsing urethral mass enlarged and was associated with increased bleeding, dysuria and left costovertebral angle pain. Physical examination revealed an acutely ill patient with an elevated temperature of 104 degrees. Examination of the vulva revealed a 2.5 cm reddish mass protruding through the urethra (Fig. 1). The mass was easily reduced by the examining finger. An IVP was performed. Preliminary film of the abdomen revealed a 1 cm ovoid laminated calculus which was located deep in the pelvis just to the left of the midline. Following the injection of opaque material, the right urinary tract seemed normal while the left urinary tract showed diminished intensity of contrast material (Fig. 2). The calculus described on the preliminary film was at the expected location of the left ureterovesical junction. At 20 minutes after injection the left upper tract and ureter showed moderate dilatation. The bladder was well distended and within its opacified shadow there was seen a 2.5 cm. rounded lucent structure in the expected location of the left ureterovesical junction (Fig. 3) An overhead radiograph was exposed with the patient in the left posterior oblique projection during the act of voiding (Fig. 4). A rounded collection of contrast material noted at the vulva was interpreted as an opacified prolapsed ureterocele; the prolapsed mass was visible clinically at this time.

Three days later the patient passed a calculus through the urethra associated with an episode of hematuria. At cystoscopy ulcerated redundant mucosa about the left ureteral orifice was interpreted as the remains of a ureterocele through whose wall a previously impacted calculus had recently eroded. Repeat intravenous pyelogram showed a persistent filling defect on the left side of the bladder but this was much smaller than the original ureterocele; further, the left tract was no longer dilated, intensity of contrast was symmetrical with the opposite side, and no opaque calculus was seen in the bladder region on the preliminary film (Fig. 5). A retrograde cystogram revealed reflux into the left ureter. The patient was treated conservatively and was discharged asymptomatic and afebrile.

Discussion

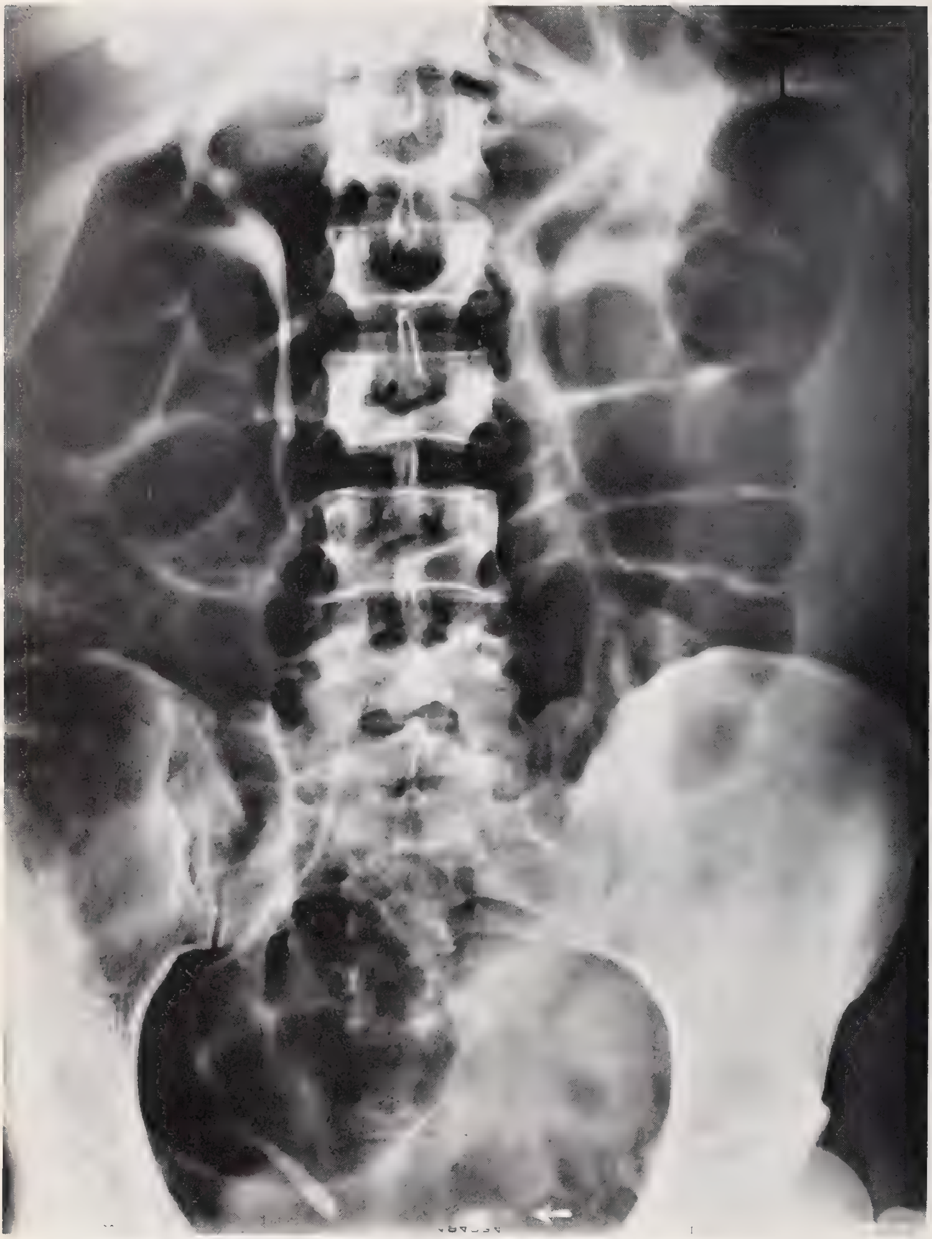
Ureterocele, a prolapse of the lower end of the ureter into the bladder through the ureterovesical orifice, has also been known as intravesical cyst of the ureter, ureterovesical cyst, or cystic dilatation of the lower end of the ureter. The condition involves all layers of the ureteral wall. The etiology and



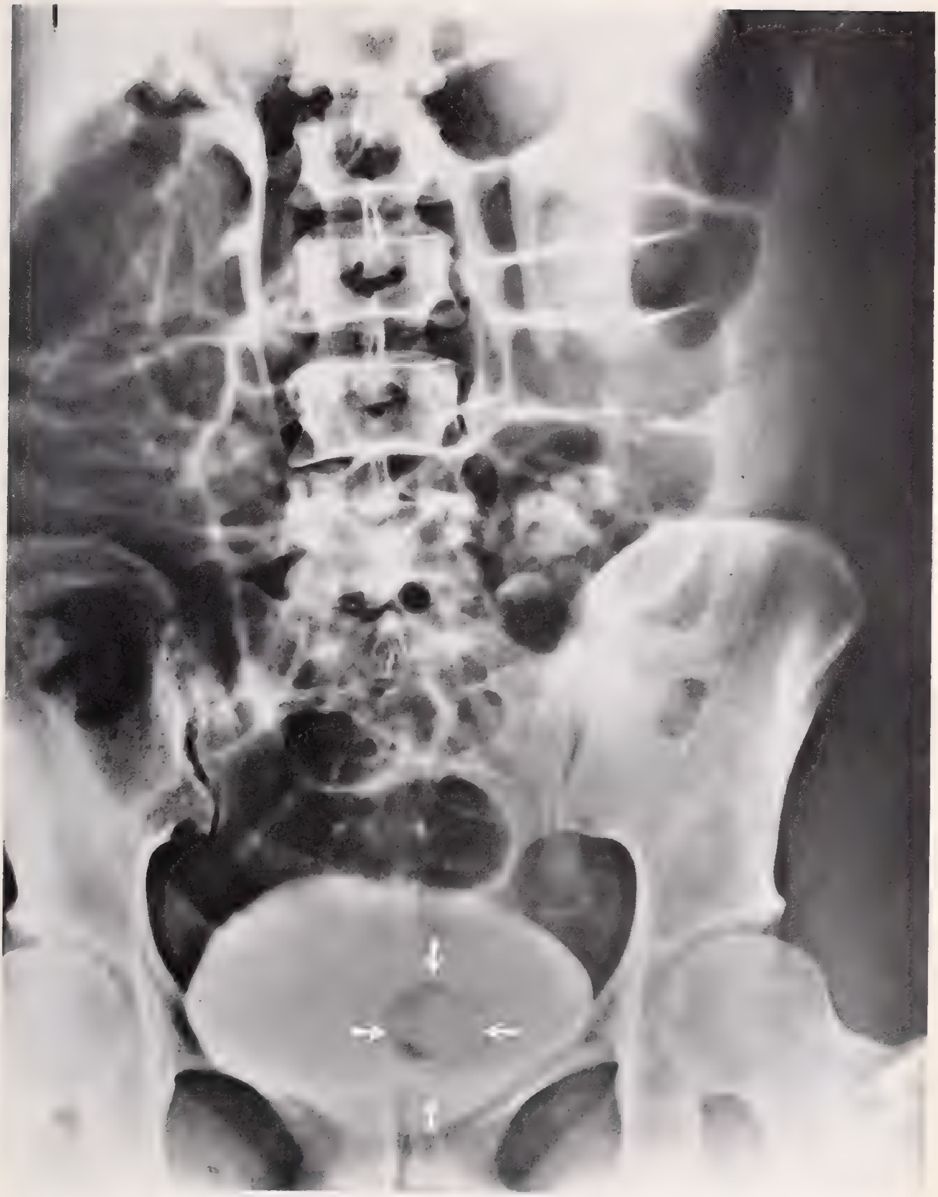
Case 387, Fig. 1. Kodachrome of the vulva reveals a 2.5 cm reddish mass of tissue protruding through the urethra.

pathogenesis of the condition are not known. The ureterocele is thought most likely to be of congenital origin: there may be a congenital stenosis at the ureterovesical junction and an associated congenital weakness of the wall of the lowermost portion of the ureter. When inflammation occurs or when the stenosis is significant the distal ureter dilates and balloons into the bladder.

Ureteroceles may be subject to many anatomic variations and complications. The simple and usual form may be unilateral, bilateral, or reduplicated on the same side associated with a duplicated collecting system. The lower end of an adjacent duplicated ureter may be compressed by the ureterocele or in some cases even a contralateral ureter may be so affected. In females, ureteroceles may prolapse from the bladder into the urethra or even externally, while in males prolapse may occur into the prostatic urethra. When associated with an ectopic ureteral orifice, the latter may be located in the urethra, in a vesical diverticulum, or end blindly in an intravesical cyst.

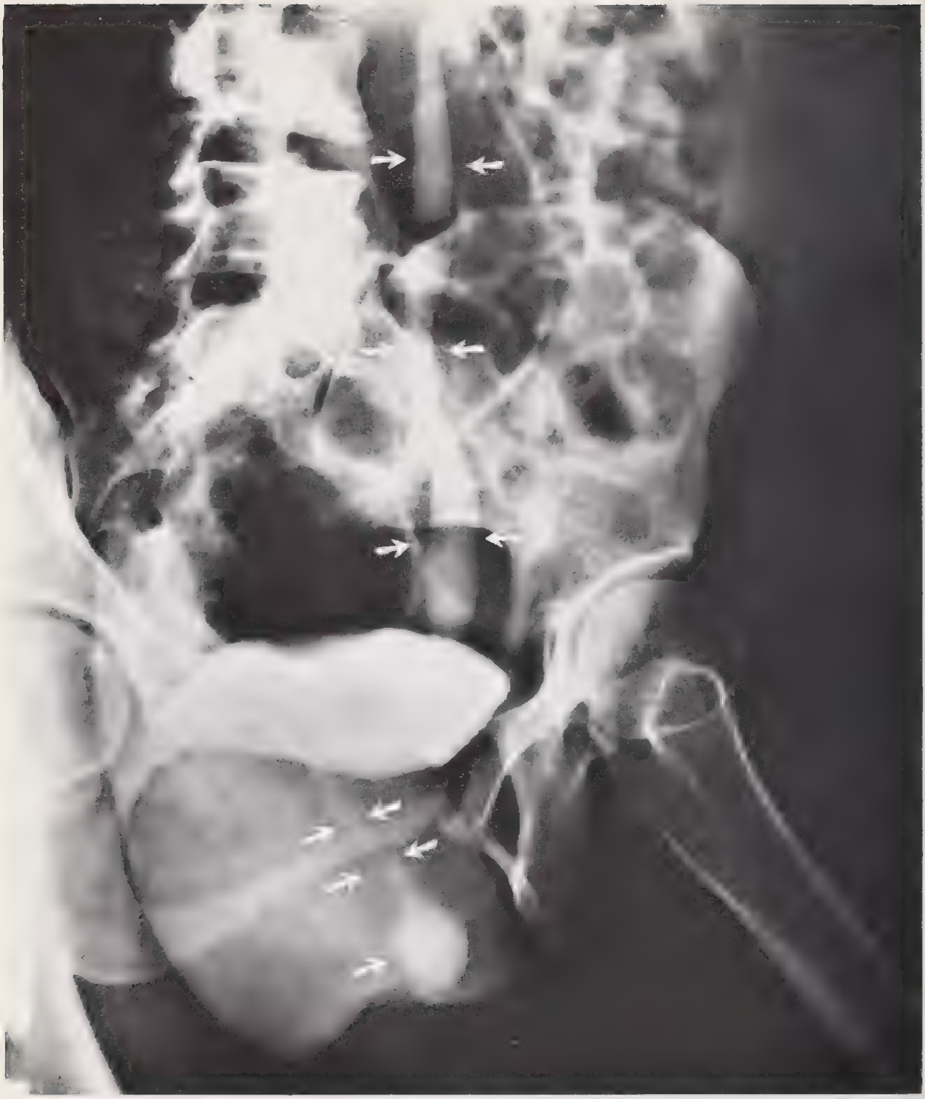


Case 387, Fig. 2. Frontal five minute film from intravenous pyelogram shows excellent visualization of the entire normal right urinary tract. The left urinary tract is visualized faintly and is slightly dilated. A 1cm ovoid calculus is seen deep in the pelvis to the left of the midline in the expected location of the left ureterovesical orifice (arrow). (An incidental biliary calculus is noted above the right kidney.)



Case 387, Fig. 3. Frontal 20-minute film from intravenous pyelogram shows a 2.5 cm rounded filling defect on the left side of the distended opacified bladder (between arrows). The left ureter is dilated although only faintly opacified.

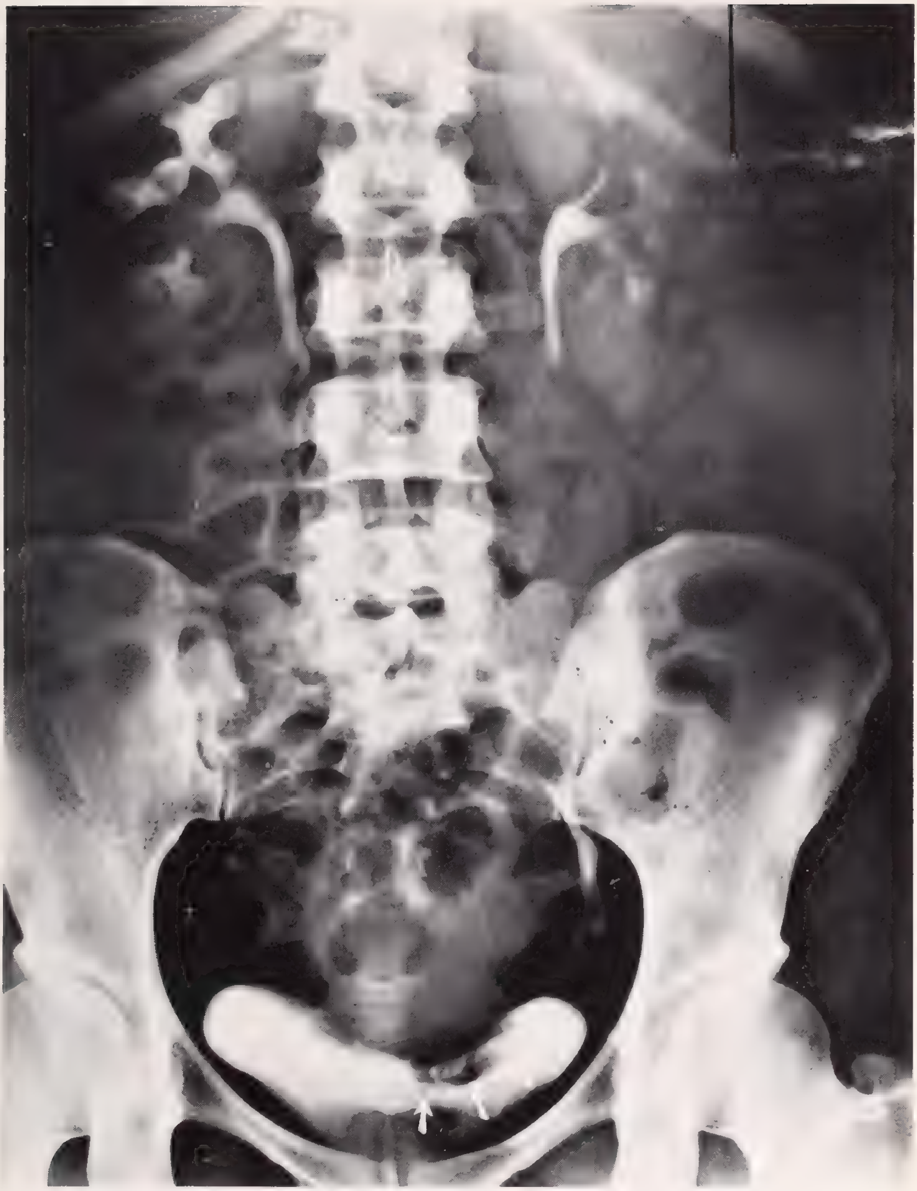
Prolapse of an ureterocele through the urethra as in the case presented is a rare occurrence. It has been described in children but is much less frequent in the adult, and it occurs virtually exclusively in the female. Stasis of urine in the ureterocele behind the narrowed meatus favors infection and stone



Case 387, Fig. 4. Overhead radiograph exposed during micturition with the patient in the left posterior oblique projection reveals the opacified ureterocele prolapsed to the vulva (lowest arrow). The calculus is obscured by contrast in the ureterocele. The prolapsed channel in the urethra between the ureterocele and the base of the bladder is faintly outlined (between lower arrows). The distinctly dilated ureter is noted to be well opacified by contrast refluxed from the bladder (between upper arrows).

formation, while the passage of stone is impeded by the stricture itself. Increased pressure accounts for the progressive nature of the condition. Ulceration and erosion of the calculus through the ureterocele in the case presented resulted in decompression of the ureterocele and improvement of the condition.

From the viewpoint of roentgen diagnosis, the examination of choice is a



Case 387, Fig. 5. Frontal 20-minute film from intravenous pyelogram shows an irregular lucency in the region of the left ureterovesical junction (arrows). This represents the remains of the ulcerated decompressed ureterocele. The left urinary tract is no longer dilated. There was no calculus seen on the preliminary film.

cystogram following an excretory urogram. A retrograde or voiding cystourethrogram may also be employed. Some disadvantages of the latter procedure should be noted: the density of the contrast material usually employed for retrograde studies may obscure detail and the size of the ballooned ureterocele may be reduced because of increased intravesical pressure produced by the retrograde injection. The principal advantage of the procedure is in cases of ureteral reflux. Here, the ureterocele and the proximal dilated ureter of a nonfunctioning segment of a duplicated collecting system may be outlined by refluxed contrast material thus establishing the diagnosis. Direct cystoscopic examination and evaluation is, of course, indicated.

Case Report: URETEROCELE PROLAPSED THROUGH THE FEMALE URETHRA.

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OPHTHALMOLOGIC NOTES

KEITH M. ZINN, M.D., Editor

Occult Ocular Melanoma

Submitted by

KEITH M. ZINN, M.D. and MARK GOLDFARB, M.D.

When evaluating a patient with unilateral cataract and glaucoma preoperatively for cataract surgery, it is important to have A & B scan ultrasonography studies performed. The following case illustrates this point:

M. Z. was a 49-year-old Caucasian male who was first seen in May, 1974, and noted to have a progressive loss of vision in his right eye over the past several years. There was no associated pain, fever, or malaise during this time. During World War II an exploding shell rendered him unconscious for several days, and he sustained trauma to the head and neck regions, including the right eye. The details of the injury and the subsequent treatment he received were not available.

The patient consulted an opthalmologist in April, 1974, who noted a "cataract and glaucoma" in the right eye. The patient was placed on Pilocarpine medication and referred for further evaluation.

Ocular examination findings were as follows: The visual acuity was hand motion at 3 feet in the right eye without correction, and 20/20-2 in the left eye with a -3.50 sphere +0.50 cylinder axis 50°. Manifest refraction could not improve the vision in either eye.

Extraocular motility studies revealed a full range of motion of either globe in all standard fields of gaze, and the eyes were straight in the primary position of gaze.

The lids, ocular adnexae, and lacrimal gland apparatus were entirely within normal limits.

Cranial nerve function I–XII was intact, bilaterally.

The right eye had 1+ erythema of the bulbar conjunctiva with a clear cornea. There were about a half-dozen fine pigment deposits noted centrally on the corneal endothelium. The right anterior chamber was clear, of moderate depth, with a grade III to IV open anterior chamber angle except from the 3:30 to 5 o'clock meridian where the angle was completely sealed. The right lens had 3+ nuclear sclerosis centrally with peripheral anterior and posterior cortical spoke-shaped opacities. The peripheral opacities were densest in the inferonasal quadrant. The cataract opacity precluded any view of the vitreous, retina, choroid, and/or optic nerve, O.D.

Intraocular pressures were 26 mm Hg in the right eye and 12 mm Hg in the left eye, by applanation tonometry.

The irides were blue, and the pupils were equal, round, and reactive to light and accommodation.

The left eye was entirely within normal limits, the anterior chamber was of moderate depth, clear, with a grade IV open angle and 1+ pigmentation of the trabecular meshwork.

A and B scan ultrasonography was performed (see Fig. 1) and a solid mass approximately 5 × 8 mm in size was noted in the region of the ciliary body in the inferonasal quadrant. The mass appeared to be in contact with the equatorial zone of the lens. The lens had increased intralenticular echoes consistent with a cataract. The anterior chamber angles were deep except in the inferonasal quadrant, where the angle was narrow. The mass appeared to be responsible for the narrow angle. The remaining portion of the ultrasonography examination, including the vitreous, retina, choroid, retrobulbar fat and optic nerve patterns, were acoustically within normal limits.

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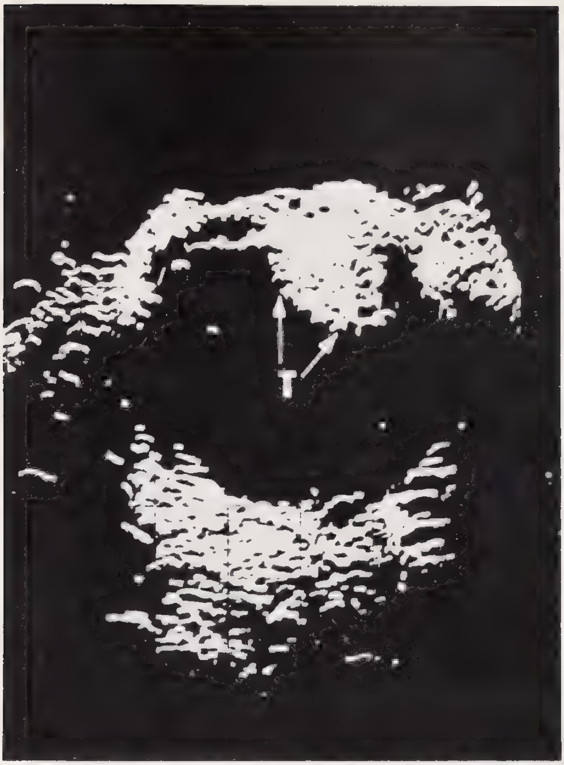

FIG. 1. B-scan ultrasonogram showing ciliary body tumor mass (T) pushing iris tissue anteriorly narrowing the anterior chamber angle in the area of the tumor.

A P^{32} uptake test was performed 48 hours after the patient received the radioactive material. The uptake ratio, comparing the lesion site (ciliary body) in the inferonasal quadrant with a comparable area in the superotemporal quadrant was 211%. This was positive for a neoplastic lesion. Also, there was poor transillumination of the lesion area compared to the other quadrants.

Physical examination revealed a well-developed, well-nourished male, in no acute distress. This examination was entirely within normal limits, including a normal chest and abdomen. No hepatomegaly was noted. The extremities were also unremarkable.

CBC, urinalysis, and 12-channel blood studies, were normal, except for a mild elevation of the serum alkaline phosphatase. Chest x-ray, metastatic bone survey, electrocardiogram, brain, and liver scans were normal. Upper GI series and barium enema studies were also unremarkable.

In June 1974, the patient underwent enucleation of the right eye and the pathology findings were as follows:

On gross examination, the right eye measured 29 × 27 × 26 mm. There was an 8 mm stump of optic nerve attached to the globe. Transillumination of the globe revealed a dense zone of pigment in the inferonasal quadrant within the ciliary body region. This lesion did not transilluminate. The eye was opened obliquely along the 10:30 o'clock and 4:30 o'clock meridians. A deeply pigmented tumor was present in the ciliary body in the inferonasal quadrant. The tumor measured 10 × 8 × 8 mm. Pigment was scattered throughout the vitreous body.

The globe was intact and there was no evidence of any episcleral extension of tumor on gross examination.

The cornea was unremarkable. The anterior chamber angle was deep, except for the inferonasal quadrant where the angle was narrow. The lens had cataract opacities, but was otherwise unremarkable.

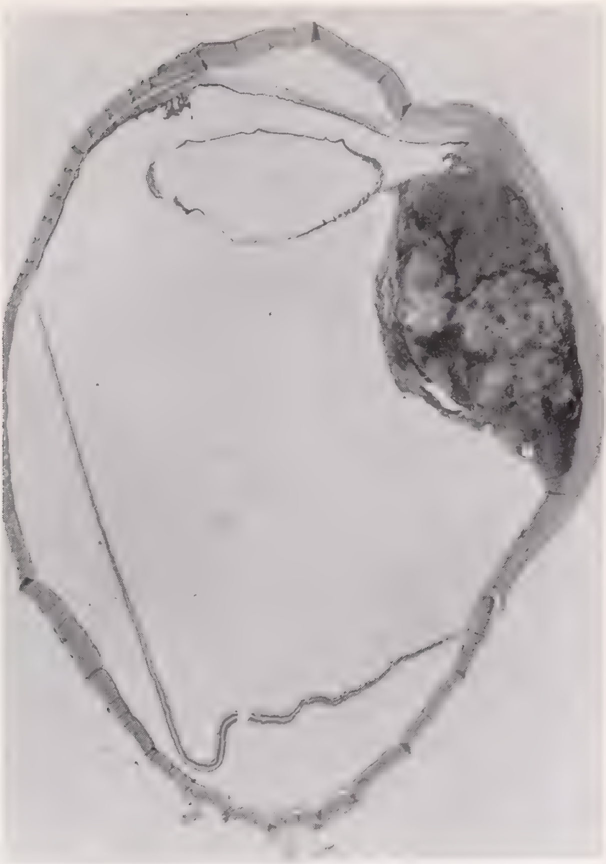

FIG. 2. Light photomicrograph showing ciliary body melanoma (6×). (Courtesy Andrew P. Ferry, M.D.)

Microscopic examination: The anterior chamber angle was sealed (inferonasal quadrant) in the region anterior to the tumor mass (Figs. 2 and 3). No tumor tissue was noted within the anterior chamber angle. The rest of the anterior chamber angle was unremarkable, and in its normal location.

The ciliary body tumor, noted on gross examination, involved the pars plicata region anteriorly, and extended within the choroid posteriorly to the equatorial region. The tumor contained tightly packed bundles of cells, whose nuclei were spindle-shaped, with ovoid nucleoli. The majority of tumor cells had considerable intracytoplasmic melanin accumulations. The tumor was not homogeneous, in that there were several foci of necrosis. At one juncture, the tumor appeared to have broken through the nonpigmented ciliary epithelium into the vitreous cavity. Pigment deposits were present in the vitreous body, as well.

The innermost layers of the sclera were heavily infiltrated with tumor, but there was no evidence of any episcleral extension of the tumor.

At the posterior border of the tumor there was extension of the tumor into the subretinal space and adjacent retina. In addition, there was a chorioretinal scar just behind the posterior edge of the tumor.

Elsewhere the general cyto-architecture of the retina and choroid appeared to be within normal limits, except for some diffuse ganglion cell loss and thinning of the nerve fiber layer, consistent with glaucoma.

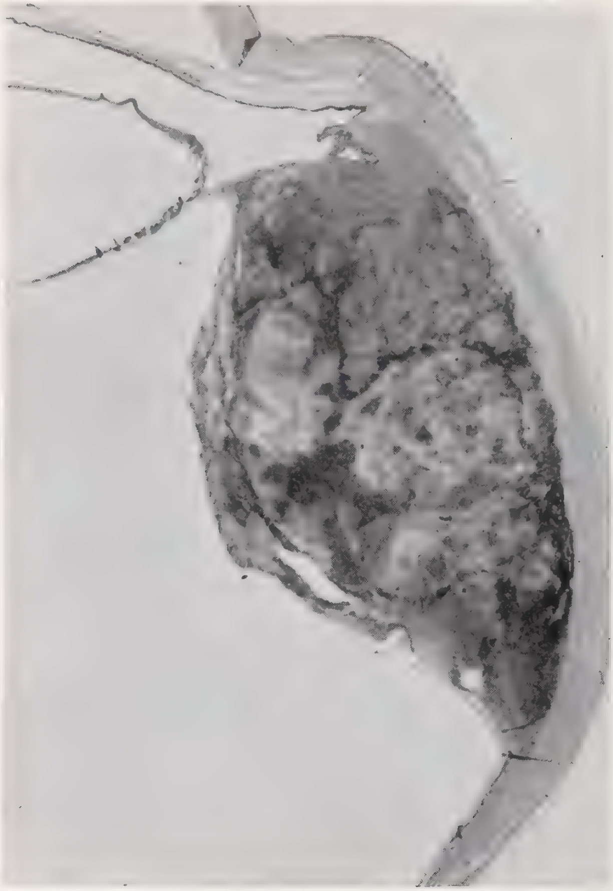

Fig. 3. Light photomicrograph of ciliary body melanoma (12 ×). (Courtesy Andrew P. Ferry, M.D.)

The optic nerve had glaucomatous cupping with some atrophy. Otherwise, the optic nerve was unremarkable.

Discussion

The major components in this case involved the development of unilateral glaucoma and cataract with progressive loss of vision in a patient with a history of antecedent trauma to that eye. However, the time course between the ocular trauma and the onset of the cataract and glaucoma was more than two decades. This should arouse one's index of suspicion with regard to the etiology of the glaucoma and the cataract. The gonioscopy findings of a narrow angle in one quadrant of an eye with a deep and open anterior chamber angle in the remaining quadrants of that eye, as well as in the other eye, point strongly to a tumor as the etiologic agent. The differential diagnosis of pigmented ciliary body tumors has been covered by Wilensky and Holland

(1974) and need not be enumerated here. Other diagnostic possibilities include lens intumescence and/or peripheral anterior synechiae secondary to uveitis, trauma, choroidal detachment, etc.

However, with a moderately dense cataract precluding any view of the posterior segment, it is essential to perform A & B scan ultrasonography as part of the diagnostic evaluation. In this case, it led to the discovery of a ciliary body tumor. The cataract extraction which was planned was deferred and a positive P^{32} test confirmed the ultrasonographic findings of a ciliary body tumor. There was no evidence of a primary malignancy elsewhere in the body, and the eye was subsequently enucleated instead of having a cataract extraction. The latter operation, if performed, could have resulted in dissemination of the tumor.

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THE STUDENT'S CORNER

JEFFREY BUCKNER, B.S., EDITOR

Medical Education Abroad

Submitted by

JUDI EHRENFELD B.A., M.A.

Of the thousands of students not accepted by American medical schools, many chose as I did to go overseas to pursue their goal of becoming a doctor. I hope a partial account of my experiences after one year at the Faculte de Medecine, Universite de Montpellier, will prove interesting.

The course of study in the French medical schools takes seven years, during which time the student studies the premedical sciences as well as the basic sciences. Clinical training is restricted to a few hours a day, three days a week in the last two years. It is not unusual for the course to take eight to ten years, depending on whether or not the student passes the exams the first time. Each student can opt to repeat any and all years.

The curriculum at Montpellier, which is the same throughout the French system of medical education, is quite different from that in the United States. Chemistry, physics, physiology, histology, cellular biology, genetics, anatomy, and embryology are all given in the first year. No laboratories are given, and these courses extend into the second and third years. Pediatrics, obstetrics and gynecology, surgery, cardiology, and pathology begin in the fourth year and continue into the fifth. Pharmacology is given in the fifth year as well. Sixth-year students have neurology, dermatology, psychiatry, and anesthesiology. The seventh year is devoted to thesis research, radiology, orthopedics, and medicine.

Classes are approximately four hours daily, there is a two-hour lunch break, and few students attend the optional afternoon discussion groups. The medical library facilities at Montpellier are extremely small, limited to French publications, open only for very limited hours and only certain days, and students are not permitted to check out materials.

For the first year of anatomy, only one session of laboratory was offered for one and a half hours. Dissection is reserved for the second-year students at which time twenty students are assigned to a single cadaver and then are split into five teams of four each. Each team is allowed to work on its cadaver once a week only, from 2:00 to 6:00 P.M. Therefore, one team can only dissect 20% of the cadaver, 80% being done by the other teams.

The composite grades on the two examinations yearly determine whether a student is promoted into the next year. If the student is not promoted and has done that year for the first time, that student can repeat the year once in order to advance. Testing of students is written for the first two years, written and oral afterwards only if the committeee has some doubt as to whether a student should be promoted based upon the written exam, and in the sixth and seventh years, the exams are exclusively oral. In addition, the student is required to do a thesis on original research in order to graduate.

Most Americans studying within the French medical system take the E.C.F.M.G. exam in the fifth or sixth year. Approximately 60% of the students pass this the first time, and almost all pass it the second time. This is the exam that allows graduates of foreign medical colleges to practice medicine in the United States. Americans try to transfer back into the American system after the third year by taking the COTRANS exam. As far as I know, not one American from Montpellier has succeeded in transferring because study of the basic sciences is not yet completed.

Many factors easily can lengthen the seven-year period for a foreigner. Most Americans do not speak the French language fluently and are not accustomed to the cultural differences. Adapting oneself to this new culture where very few people speak your language and do things the way that you do is no easy matter. As a first-year student, you very quickly find out that there are about 2,000 others in your class competing for 350 places in the second year. If you don't speak the language and have trouble taking care of day-to-day living, your chances are not high, especially when you consider that a large proportion of the class is made up of those who have not been promoted from the year before.

Studying overseas is a tremendously trying experience. Of course there are schools in other countries that are not like this one, but I would strongly urge anyone considering this course to investigate thoroughly all aspects of the particular schools involved. When I questioned the French consulate in New York about the curriculum and student life, I was given only a small pamphlet describing the curriculum in the most general terms.

My advice to anyone considering going overseas to study medicine is to be fully aware of the sacrifices required to get a foreign medical degree. I would suggest choosing a school with a somewhat large American population of students, because they will help you enormously with your initial period of adaptation. Moreover, the administration of the school is apt to be more responsive to the needs of the American population. You must also be aware that graduating from a foreign school does not guarantee that you will be able to practice medicine in the United States. The prospect of going back in October to spend another six years in Montpellier is very distasteful, and I have many hopes and plans that I will be able to complete my education at an American school. That dream is something that I certainly share with all American students in my situation.

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Letter to the Editor*

PATHOLOGIST'S DIAGNOSIS/SURGEON'S DILEMMA

Dear Sir:

Seeking the optimum surgical treatment of breast carcinoma is the main endeavor of numerous current clinical studies. Several institutions have attempted to demonstrate that lesser surgical procedure, lumpectomy or partial mastectomy is as good or better than more radical surgery. Their presentations concentrate on surgical techniques with the consequential survival data. Seldom are the pathologic criteria of breast carcinoma stated by them. Is it possible that pathologists at one institution may be more liberal in their diagnosis of carcinoma than pathologists at another institution? Is it possible that the five-year survival statistics of certain institutions are not a reflection of the proficiency of their surgical technique, but a reflection of the standards of their pathology department? If the pathologist diagnoses lesions of low virulence as carcinoma, then the eventual surgical procedure applied to these patients will have a very high cure rate. Obviously the reverse is true. A recent patient exemplifies this discrepancy.

A. F. was a 46-year-old woman who in March 1967 had a small, firm, well-circumscribed lesion in the upper outer quadrant of each breast. They were nontender, nonadherent and each measured approximately one centimeter in diameter. Axillary lymph nodes were not palpable. Both lesions were excised. The pathologic diagnosis written by the senior pathologist read: "Right breast showed multiple focal ductal hyperplasia, marked epithelial proliferation. However, no hyperchromatism, cell atypism, and mitosis found. No evidence of malignancy. Left breast identical lesion, however, less extensive."

This patient was under constant observation and in December 1971 it was noted she had two new small lesions in the right breast. One was located in the upper outer quadrant and the other in the lower inner quadrant. These lesions were similar to those occurring four and a half years previously. They were round, well-circumscribed, nontender, not adherent, and approximately one centimeter in diameter. During this second admission the patient was entered into the National Surgical Adjuvant Breast Protocol. Excisional biopsies were performed with a frozen section report of infiltrating carcinoma in each specimen. A radical mastectomy was performed, in accordance with the protocol designation.

The original pathologist who examined the specimens of 1967 died and his

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* Letters should be clearly marked "For Publication" and will be published at the discretion of the Editor and as space permits. Letters are subject to editing. Letters for publication should include name, degree, chief institutional affiliation and address of author. Mail letters to: *Editor*, The Mount Sinai Journal of Medicine, The Annenberg Building, Room 10-35, Fifth Avenue and 100th Street, New York, N. Y. 10029.

successor diagnosed the specimens of 1971. The second pathologist then stated that this patient was ineligible to be entered into the National Surgical Adjuvant Breast Protocol because she had a previous breast carcinoma, which automatically eliminated her. He reported that he reviewed the original slides and rediagnosed the allegedly benign lesions as malignant.

To date, eight years after the initial bilateral excisional biopsies and three and a half years after the radical mastectomy, this patient is well and without evidence of recurrence or progression of disease. If one adheres to the criteria of the original pathologist, the patient has been cured and the radical mastectomy was unnecessary. If the surgeon adheres to the second pathologist, then lumpectomy can be an excellent mode of therapy for carcinoma and the right radical mastectomy was unnecessary.

This example involves two pathologists at the same institution reporting a different diagnosis on the same breast specimens. It becomes apparent that a liberally applied diagnosis of carcinoma will lead to a high success rate even if only a lumpectomy is performed. It behooves the surgeon to ascertain the criteria utilized by the pathology department of his institution in the diagnosis of breast carcinoma because this may influence his decision in the choice of the surgical procedure. It also demonstrates that only double-blind studies within an institution should be utilized for comparison of clinical studies.

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Editorial Statement

The scholarly work on the following pages is the first addendum ever published by our Journal. We hope to be able to provide prestigious dissemination for scientific material that is too large for a single paper, but too small for a monograph.

Our goal is quality; our only limitation is financial. Therefore, the additional publishing costs for these supplements must be met by private or institutional sources other than our own Medical Center budget. Some of the supplements will be published separately from the regular issue, but the financial constraints will be the same.

Nevertheless, we feel it is the duty of the Mount Sinai Journal to make some small effort to present scholarly but commercially unfeasible work to the general scientific community.

David A. Dreiling, M.D.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 42, No. 6, November-December, 1975
Printed in U.S.A.

INDEX TO VOLUME FORTY-TWO

ABORTION
  (M. S. Burnhill), 431
  (J. D. Osofsky et al), 456
  (D. P. Schwartz), 468
Adamsons, K et al. Disseminated intravascular coagulation, 415
Adolescent
  Guidance program in contraception motivation. (S. B. Gusberg et al), 439
  Intrauterine contraception. (M. E. Lane et al), 337
  Parents. (J. B. Nettles et al), 452
  Psychosexual disturbances in girls. (F. Brown), 216
Adrenocortical disorders related to the biosynthesis and regulation of steroid hormones and their computer simulation. (D. C. Sharma et al), Supplementum to Nov-Dec 1975 issue, S1
Amylophagia during pregnancy. (D. Keith et al), 410
Anal fissure, lateral subcutaneous internal sphincterotomy. (C. Oh), 596
Anderson, R. K. Family planning and malaria control: some parallels, 256
Afterloading in cancer of cervix. (N. Simon et al), 565
Air embolism. (Y.-M. Rho et al), 245
Alcoholic pancreatitis. (H. Sarles et al), 540
Angiography and Egas Moniz. (A. R. Damásio), 502
Anorexia in female adolescents. (F. Brown), 216

BANK, S. Small bowel structure and function in pancreatic steatorrhea, 552
Barnes, A. C. Population growth and the quality of life, 265
Beck, A. R. (*See* Unusual Problems in Surgery)
Beck, A. R. et al. Preoperative diagnosis of Meckel's diverticulum, 136
Bellin, L. E. Cloud nine academe and the trenches of health administration, 514
Berenstein, A.
  Displacement and reorientation of a staghorn calculus, 602
  Ureterocele prolapsed through the female urethra, 608
Berger, G. S. et al. Amylophagia during pregnancy, 410
Berman, A. J. et al. Thyroid carcinoma, 207
Biel, L., Jr. Obituary: Dr. Gordon D. Oppenheimer, 177
Bloch, C. (*See* Radiologic Notes)
Bochdalek hernia presenting at one year of age. (A. R. Beck), 173
Borror, A. D. et al. Supplementum to Nov-Dec 1975 issue. A study of adrenocortical disorders related to the biosynthesis and regulation of steroid hormones and their computer simulation, S1
Breast
  Carcinoma in a husband and wife. (B. B. Wetchler et al), 205
  Chondroblastic sarcoma of. (S. D. Gisser et al), 232
Brown, F. Adolescent psychosexual disturbances, 216
Buckner, J. (*See* The Student's Corner)
Burnhill, M. S. Humane abortion services, 431

CAMERON, O. et al. Adolescent guidance program in contraception motivation, 439
Campomanes, B. A. et al. Coxsackie hepatitis in an adult, 575
Carcinoma
  Breast, in husband and wife. (B. B. Wetchler et al), 205
  Endometrial. (D. K. Sirota et al), 586
  Thyroid. (R.A. Brodner et al), 207
Casey, G. et al. Twin gestation, 523
Cefazolin, clinical studies. (G.S. Hammer et al), 142
Cervical cancer, afterloading. (N. Simon et al), 565
Chondroblastic sarcoma of the breast. (S. D. Gisser et al), 232
Chuang, M. et al. Application of flexible bronchoscope, 81
Cobb, J. C. et al. Recruiting the uncommitted leader for family planning, 308
Colonoscopy. (J. Waye et al), 1–94
Contraception
  (M. E. Lane et al), 337
  (H. Lehfeldt), 345
  (J. Lippes et al), 353
  (R. J. Pion), 364
  (H. Schulman), 367
  (C. F. Westoff et al), 384
  (J. E. Davis et al), 391
  (S. B. Gusberg et al), 439
Corsa, L. Family planning associations and development of population policy and programs, 269
Cortese, C. F. et al. Recruiting the uncommitted leader for family planning, 308
Cox, L. et al. Adolescent guidance program in contraception motivation, 439
Coxsackie hepatities in an adult. (G. R. Gregor et al), 575
Cryohemorrhoidectomy. (C. Oh), 179
Cytosarcoma phyllodes. (S. D. Gisser et al), 232

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DAMÁSIO, A. R. Egas Moniz, pioneer of angiography and leucotomy, 502
Davis, M. J. Guillain-Barré variant: ophthalmoplegia, ataxia and areflexia, 167
Davis, J. E. et al. Vasectomy, 391
De Persio, S. R. et al. Comprehensive programs for school-age parents, 452
Diabetes in pregnancy. (J. W. Greene, Jr.), 398
Diethylstilbestrol treatment in Turner's syndrome. (D. K. Sirota et al), 586
Disseminated intravascular coagulation. (E. Mueller-Heubach et al), 415
Dying patient. (L. J. Roose et al), 99

EDITORIAL. Salute to Dr. Steven Podos. (K. Zinn), 501
Ehrenfeld, J. Medical education abroad, 620
Embolism
  Air. (Y.-M. Rho et al), 345
  Amniotic fluid. (E. Mueller-Heubach et al), 415
Endoscopy. (J. Waye et al), 1–94
Estriol. (J. W. Greene, Jr.), 398

FAMILY planning (*See* population and family planning)
Fayemi, A. O. Lung in systemic lupus erythematosus, 110
Fertility
  Research. (S. J. Segal), 375
  Sterility. (S. Katsh et al), 405
Figarella, C. et al. Alcoholic pancreatitis, 540
Flexible bronchoscopy. (A. S. Teirstein et al), 81
Foot, J. et al. Amylophagia during pregnancy, 410

GABRILOVE, J. L. et al. Supplementum to Nov-Dec 1975 issue. A study of adrenocortical disorders related to the biosynthesis and and regulation of steroid hormones and their computer simulation, S1
Gall bladder perforation. (P. J. Wilk), 119
Gastrojejunocolic fistula, modern concepts in management of. (J. Hodgson et al), 239
Gatchell, L. H. et al. Comprehensive programs for school-age parents, 452
Geller, S. A. et al Coxsackie hepatitis in an adult, 575
Gichon, G. et al. Preoperative diagnosis of Meckel's diverticulum, 136
Gisser, S. D. et al. Chondroblastic sarcoma of the breast, 232
Gold, E. M. Maternal and child health and family planning services, 277
Goldfarb, M. et al. Occult ocular melanoma, 615
Goldstein, H. et al. Infant mortality in Sweden: implications for US, 479
Greene, J. W., Jr. Diabetes mellitus in pregnancy, 398
Gregor, G. R. et al. Coxsackie hepatitis in an adult, 575
Guillain-Barré variant: ophthalmoplegia, ataxia and areflexia, 167
Gusberg, S. B. et al. Therapeutic listening in adolescent guidance program in motivation for contraception, 439

HAMMER, G. S. et al. Clinical studies with cefazolin, 142
Health
  Administration. (L. E. Bellin), 514
  Insurance for reproduction. (C. Muller), 316
  Maternal and child and family planning services. (E. M. Gold), 277
Hellman, L. M. et al. Letter to Alan Guttmacher on World Population Conference, Bucharest, Romania, 1974, 492
Hemorrhoidectomy by cryotechnique. (C. Oh), 179
Hilsen, J. et al. Adolescent guidance program in contraception motivation, 439
Hirschman, S. Z. et al. Clinical studies with cefazolin, 142
Hodgson, J. et al. Management of gastrojejunocolic fistula, 239
Hyperalimentation, preoperative. (J. Hodgson et al), 239

ILEOCOLIC intussusception presenting as left upper quadrant mass, masquerading as a pancreatic pseudocyst. (E. J. Mencer et al), 581
Infant mortality in Sweden. (H. M. Wallace et al), 479
Ischemic colitis. (P. J. Wilk), 119

JAFFE, F. S. Social history and Planned Parenthood Federation, 286
Jones, E. F. et al. Discontinuation of the pill and IUD in US: 1960–1970, 384

KAISER, I. H. Alan Guttmacher and family planning in Cuba, 300
Katsh, G. F. et al. Immunochemistry of a reproductive antigen involved in sterility and fertility, 405
Katsh, S. et al. Immunochemistry of a reproductive antigen involved in sterility and fertility, 405
Keith, D. et al. Amylophagia during pregnancy, 410
Keith, L. et al. Amylophagia during pregnancy, 410
Keratoacanthoma. (J. Kwittken), 127
Keratocarcinoma. (J. Kwittken), 127
Kohl, S. G. et al. Twin gestation, 523
Kwittken, J. Chronology of keratocarcinoma, 127

LAMINARIA tent. (K. R. Niswander), 424
Lane, M. E. et al. Intrauterine contraception

by adolescent women, 337
Langmyhr, G. J. et al. Alan F. Guttmacher's role in teaching human sexuality, 445
Laparotomy in fever of unknown etiology. (S. Wilkinson), 236
Leaver, F. W. et al. Immunochemistry of a reproductive antigen involved in sterility and fertility, 405
Lee, H. K. et al. Preoperative diagnosis of Meckel's diverticulum, 136
Lehfeldt, H. Ernst Gräfenberg and his ring, 345
Letter to the Editor.
  Pathologist's diagnosis/surgeon's dilemma. (B. B. Wetchler), 622
Leucotomy and Egas Moniz. (A. R. Damásio), 502
Lief, H. I. et al. Alan F. Guttmacher's role in teaching human sexuality, 445
Lippes, J. et al. The Loop Decade, 353
Loh, C. et al. Ileocolic intussusception, 581
Low birthweight
  Amylophagia. (D. Keith et al), 410
  Twin gestation. (S. G. Kohl et al), 523
Lubell, I. et al. Vasectomy, 391
Lung in systemic lupus erythematosus. (A. O. Fayemi), 110
Lusins, J. (*See* Neurologic Notes)
Lusins, J. et al. (*See* Neurologic-Neurosurgical Notes)
Lyons, A. S. Aids to the surgeon by mammography, 223

MALIGNANT chondroblastoma. (S. D. Gisser et al), 232
Malis, L. I. et al. Von Hippel-Lindau's disease, 245
Mammography, aids to the surgeon. (A. S. Lyons), 223
Marinoff, S. C. et al. Endometrial carcinoma in Turner's syndrome following DES treatment, 586
Marinoff, S. et al. Adolescent guidance program in contraception motivation, 439
Marvin, E. A. et al. Comprehensive programs for school-age parents, 452
McElhinney, A. J. et al. Ileocolic intussusception, 581
Meckel's diverticulum, preoperative diagnosis. (H. K. Lee et al), 136
Medina, O. F. et al. Management of gastrojejunocolic fistula, 239
Melanoma, occult ocular. (K. M. Zinn et al), 615
Mencer, E. J. et al. Ileocolic intussusception, 581
Messe, A. et al. Management of gastrojejunocolic fistula, 239
Meyers, B. R. et al. Clinical studies with cefazolin, 142
Miller, A. et al. Application of flexible bronchoscope, 81
Moniz, Egas, pioneer of angiography and leucotomy. (A. R. Damásio), 502
Moulding, T. S. et al. Recruiting the uncommitted leader for family planning, 308
Mueller-Heubach, E. et al. Disseminated intravascular coagulation, 415
Muller, C. Financial assurance for reproductive health services, 316
Myers, R. E. et al. Disseminated intravascular coagulation, 415

NAKAGAWA, H. et al. Thyroid carcinoma, 207
Nathan, D. M. Respiratory distress syndrome, 150
Nettles, J. B. et al. Comprehensive programs for school-age parents, 452
Neurologic Notes, J. Lusins, editor
  A Guillain-Barré variant: ophthalmoplegia, ataxia and areflexia (A. J. Davis), 167
Neurologic-Neurosurgical Notes, J. Lusins and M. H. Savitz, coeditors
  Von Hippel-Lindau's disease. (Y.-M. Rho et al), 245
Nipper, T. et al. Preoperative diagnosis of Meckel's diverticulum, 136
Niswander, K. R. Modern use of the laminaria tent, 424

OBITUARIES
  Colp, Dr. Ralph, 95
  Oppenheimer, Dr. Gordon D., 177
Occult ocular melanoma. (K. M. Zinn et al), 615
Oh, C.
  Cryohemorrhoidectomy, 179
  Lateral subcutaneous sphincterotomy for anal fissure, 596
Ophthalmologic Note. K. M. Zinn, editor
  Occult ocular melanoma. (K. M. Zinn et al), 615
Osofsky, H. J. et al. Psychosocial aspects of abortion in US, 456
Osofsky, J. D. et al. Psychosocial aspects of abortion in US, 456

PANCREATIC
  pseudocyst. (E. J. Mencer et al), 581
  Steatorrhea, small bowel structure and function in (S. Bank), 552
Pancreatitis, alcoholic. (H. Sarles et al), 540
Peck, H. M. (*See* Radiologic Notes)
Peptic ulcer complications. (J. Hodgson et al), 239
Pheochromocytoma. (Y.-M. Rho et al), 245
Pion, R. J. Contraception and society, 364
Planned Parenthood Federation of America. (F. S. Jaffe), 286
Planned parenthood and natural law. (M. Potts), 326
Population and family planning

  (R. K. Anderson), 256
  (A. C. Barnes), 265
  (L. Corsa), 269
  (E. M. Gold), 277
  (F. S. Jaffe), 286
  (L. M. Hellman et al), 492
  (I. H. Kaiser), 300
  (T. S. Moulding et al), 308
  (C. Muller), 316
  (M. Potts), 326
  (B. Viel), 335
Postpartum bleeding. (E. Mueller-Heubach et al), 415
Potts, M. Natural law and planned parenthood, 326
Pregnancy
  Amylophagia. (L. Keith et al), 410
  Diabetes. (J. W. Greene, Jr.), 398
  Twin gestation. (S. G. Kohl et al), 523
  Use of laminaria tent. (K. R. Niswander), 424
Prothro, G. W. et al. Comprehensive programs for school-age parents, 452
Psychosexual disturbances in adolescent girls. (F. Brown), 216

RADIOLOGIC Notes, C. Bloch and H. M. Peck, Coeditors
  Displacement and reorientation of a staghorn calculus. (A. Berenstein), 602
Ureterocele prolapsed through the female urethra. (A. Berenstein), 608
Rajan, R. et al. Psychosocial aspects of abortion in US, 456
Respiratory distress syndrome. (D. M. Nathan), 150
Rho, Y.-M. et al. Von Hippel-Lindau's disease, 245
Ribner, B. S. et al. Clinical studies with cefazolin, 142
Roose, L. J. et al. Every step of the way, 99
Rovinsky, J. J. et al
  Editors' note, 255
  Guest editor, vol. 42, nos. 4 and 5, 1975. Alan F. Guttmacher memorial issue, 255–390 and 391–491

SACHDEV, V. P. et al. Von Hippel-Lindau's disease, 245
Sarles, H. et al. Alcoholic pancreatitis, 540
Schulman, H. Prostaglandins in conception control, 367
Schwartz, I. S. et al. Preoperative diagnosis of Meckel's diverticulum, 136
Segal, S. J. Fertility research, 375
Sharma, D. C. et al. Supplementum to Nov-Dec 1975 issue. A study of adrenocortical disorders related to the biosynthesis and regulation of steroid hormones and their computer simulation, S1
Silverstone, S. M. et al. Afterloading in cancer of the cervix, 565
Simon, B. Obituary: Dr. Ralph Colp, 95
Simon, B. et al. Breast carcinoma in a husband and wife, 205
Simon, N. et al. Afterloading in cancer of cervix, 565
Sirota, D. K. et al. Endometrial carcinoma in Turner's syndrome following DES treatment, 586
Small bowel structure and function in pancreatic steatorrhea. (S. Bank), 552
Sobrero, A. J. et al. (intrauterine contraception by adolescent women, 337
Spinal cord hemangioblastoma. (Y.-M. Rho et al), 245
Spitz, D. et al. Psychosocial aspects of abortion in US, 456
Starch ingestion. (D. Keith et al), 410
Student's Corner, The. J. Buckner, editor
  Medical education abroad. (J. Ehrenfeld), 620
  Multiple choice examinations in medical school, 252
Supplementum to Nov-Dec 1975 issue. A study of adrenocortical disorders related to the biosynthesis and regulation of steroid hormones and their computer simulation. (D. C. Sharma et al), S1
Swartz, D. P. Impact of voluntary abortion on American obstetrics and gynecology, 468
Systemic lupus erythematosus, the lung. (A.O. Fayemi), 110

TEIRSTEIN, A. S. et al. Application of flexible bronchoscope, 81
Teodorescu, M. et al. Management of gastrotrojejunocolic fistula, 239
Thyroid carcinoma presenting as epidural metastasis with spinal cord compression. (R. A. Brodner et al), 207
Tietze, C. et al
  Editors' note, 255
  Guest editor, vol. 42, nos. 4 and 5, 1975, Alan F. Guttmacher memorial issue, 255–390 and 391–491
Tiscornia, O. et al. Alcoholic pancreatitis, 540
Toker, C. et al. Chondroblastic sarcoma of the breast, 232

ULTRASTRUCTURAL demonstration of Coxsackie hepatitis in an adult. (G. R. Gregor et al), 575
Unusual Problems in Surgery. A. R. Beck, editor
  Bochdalek hernia presenting at one year of age, 173

VON HIPPEL-LINDAU'S disease. (Y.-M. Rho et al), 245

Viel, B. Remembrance of Alan F. Guttmacher by a Latin American physician, 335

WALKER, G. F. et al. Coxsackie hepatitis in an adult, 575

Wallace, H. M. et al. Infant mortality in Sweden: implications for US, 479

Waye, J. D., guest editor, vol. 42. no. 1, 1975, Current Status of Flexible Fiberoptic Endoscopy, 1–94

  Colonoscopy: a clinical view, 1

  Endoscopic visualization of pancreatic and biliary ducts, 35

  Current status of esophagoscopy, gastroscopy, and duodenoscopy, 57

Webster, A. et al. Amylophagia during pregnancy, 410

Weinberger, C. W. et al. Letter to Alan Guttmacher on World Population Conference, Bucharest, Romania, 1974, 492

Westoff, C. F. et al. Discontinuation of the pill and IUD in US: 1960-1970, 384

Wetchler, B. B. Pathologist's diagnosis/surgeon's dilemma (letter to the editor), 622

Wetchler, B. B. et al. Breast carcinoma in a husband and wife, 205

Wilk, P. J. Ischemic colitis with perforation into gall bladder, 119

Wilkinson, S. Exploratory laparotomy in fever of unknown etiology, 236

Wisniewski, M. et al. Thyroid carcinoma, 207

YOUNG, A. et al. Adolescent guidance program in contraception motivation, 439

ZELEZNY, M. et al. The Loop Decade, 353

Zinn, K. M.

  Salute to Dr. Steven Podos, 501

  (*See* Ophthalmologic Note)

Zinn, K. M. et al. Occult ocular melanoma, 615

Zucker, H. D. et al. Every step of the way, 99

SUPPLEMENTUM I

1975

A STUDY OF THE ADRENOCORTICAL DISORDERS RELATED TO THE BIOSYNTHESIS AND REGULATION OF STEROID HORMONES AND THEIR COMPUTER SIMULATION

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A Study of the Adrenocortical Disorders Related to the Biosynthesis and Regulation of Steroid Hormones and their Computer Simulation

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Abstract

The production of cortisol and aldosterone by the adrenal cortex involves a succession of "enzyme systems." This study presents an integrated quantitative view of these successive biosynthetic steps and their importance in clinical disorders related to an excess or deficiency of these hormones.

A numerical digital computer model has been used to study the modulation of the biosynthesis and secretion of these hormones under physiological and certain pathological conditions. Biochemically based hypotheses for the structure of the adrenocortical system and enzymatic rate equations, including the effects of inhibition, stimulation, and feedback regulations, form the basis of it.

In humans, physiologically, the main hormones secreted by the adrenal cortex are cortisol and aldosterone, although the adrenal cortex also is capable of secreting "adrenal androgens" and estrogens. Ordinarily this latter contribution is modest compared to that of the gonads, but under certain circumstances the secretion of sex hormones by the adrenal cortex is of clinical significance. The common biosynthetic pathways (87) shared by the adrenal cortex and the gonads probably reflect the common embryologic origin of these endocrine organs in the urogenital ridge (39).

The biosynthesis of cortisol and aldosterone involves a succession of "enzyme systems." To function properly, such multi-enzyme systems have self-regulating and self-adjusting properties that are the consequence of their sequential organization, of specific properties of the individual component enzymes, and of feedback and other types of regulations by inhibition or stimulation of certain steps in the chain. In the biosynthesis of cortisol and aldosterone similar controls have also been observed (81, 88, 89).

Biosynthesis of Adrenocortical Hormones

To obtain leads to further inquiry and plausible answers to questions of current interest, we have attempted an integrated quantitative view of the biosynthetic processes in the adrenal cortex. The purpose of the model is to act as a stand-in for the actual system so that quantitative results can be observed by simulation for experiments that are impractical, difficult, or too expensive to carry out *in vivo*.

The emphasis is on key enzyme reactions in the biosynthesis of cortisol and

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LIST OF SYMBOLS AND ABBREVIATIONS

Compound B = Corticosterone or 11β,21-dihydroxy-pregn-4-ene-3, 20-dione
18-OH-corticosterone = 18 Hydroxycorticosterone or 11β, 18, 21-trihydroxy-pregn-4-ene-3, 20-dione or 18-OH-B.
DOC = 11-Deoxycorticosterone or 21-hydroxy-pregn-4-ene-3,20-dione.
Aldo = Aldosterone or 11β, 21-dihydroxy-3, 20-dioxo-pregn-4-en-18-al (18→11) hemiacetal.
Dhea = Dehydroepiandrosterone or 3β-hydroxy-androst-5-en-17-one.
Δ^4-Dione = Androstenedione or androst-4-ene-3, 17-dione.
Prog = Progesterone.
Pregn = Pregnenolone or 3β-hydroxypregn-5-en-20-one.
Compound S = 11-Deoxycortisol or 17α, 21-dihydroxypregn-4-ene-3, 20-dione.
Cortisol = 11β, 17α, 21-Trihydroxypregn-4-ene-3, 20-dione.
ACTH = Adrenocorticotropic hormone.
d/dt = Differentiation with respect to time.

Greek Letters

α - alpha
β - beta

aldosterone and their importance in disorders related to an excess or deficiency of these hormones. To keep the model tractable, the following simplifying assumptions were necessary:

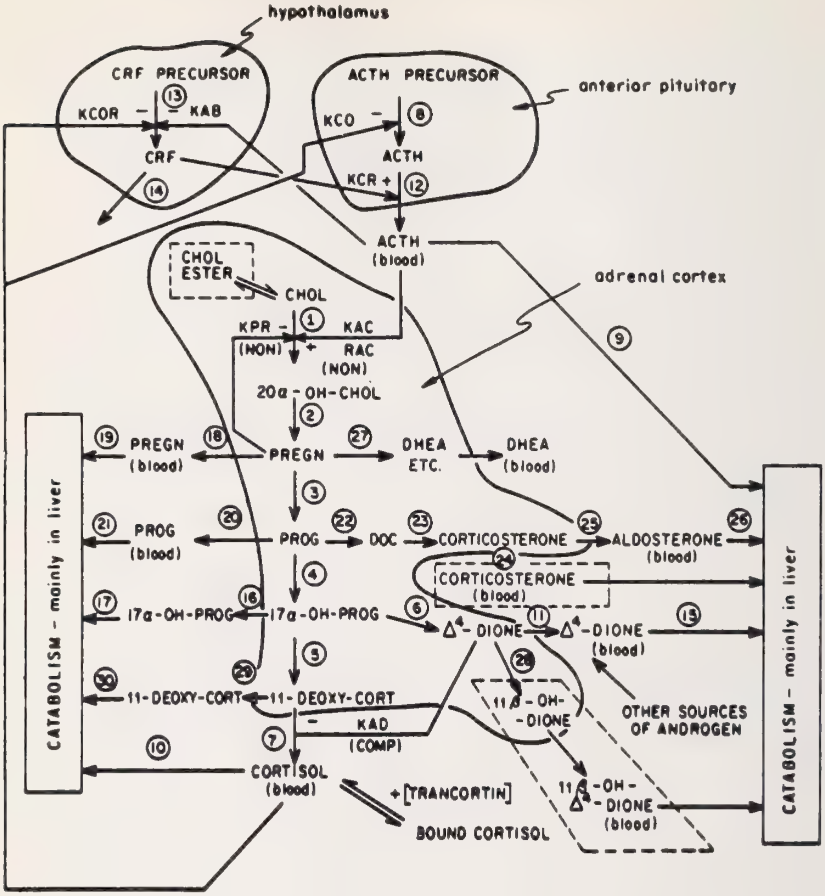
1. Only the principal pathways have been incorporated; aldosterone and androgen biosynthesis have been considered insofar as they affect cortisol production. The possibilities of alternative pathways and mechanisms involving transient complexes in the hydroxylation of the steroid nucleus do exist and are recognized; but these have not been incorporated.
2. It is recognized that experimental conditions and species variations limit the applicability of kinetic parameter values reported in the literature. However, since these experimental studies have helped various investigators in determining and explaining certain endocrine disorders when available, the reported parameters have been taken into consideration.
3. The enzyme activity is modulated primarily by stimulation or inhibition through competitive or noncompetitive types of mechanisms. The biosynthetic processes occur in a volume of 6 ml; the volume of the circulatory system is 6 liters.

Biosynthetic Reactions

Although the sequence of these reactions is not completely known, Figure 1 summarizes the major steps generally accepted today. Other principal organs involved in influencing the levels of cortisol in peripheral blood have also been included.

1. Role of Cholesterol as a Precursor of Steroids

Although steroid hormones may be synthesized from small molecules, such as acetate, cholesterol is considered the immediate precursor under many


hypothalamus
CRF PRECURSOR
⑬
KCOR
KAB
CRF
⑭
ACTH PRECURSOR
anterior pituitory
KCO
⑧
ACTH
KCR +
⑫
ACTH (blood)
CHOL ESTER
CHOL
adrenal cortex
⑨
KPR
①
KAC
(NON)
RAC (NON)
20α-OH-CHOL
②
⑲
PREGN (blood)
⑱
PREGN
㉗
DHEA ETC.
DHEA (blood)
③
CATABOLISM - mainly in liver
㉑
PROG (blood)
⑳
PROG
㉒
DOC
㉓
CORTICOSTERONE
㉕
ALDOSTERONE (blood)
㉖
㉔
CORTICOSTERONE (blood)
④
⑰
17α-OH-PROG
⑯
17α-OH-PROG
⑥
Δ⁴-DIONE
⑪
Δ⁴-DIONE (blood)
⑮
⑤
㉘
㉚
11-DEOXY-CORT
㉙
11-DEOXY-CORT
11β-OH-Δ⁴-DIONE
OTHER SOURCES OF ANDROGEN
KAD (COMP)
⑦
⑩
CORTISOL (blood)
+[TRANCORTIN]
BOUND CORTISOL
11β-OH-Δ⁴-DIONE (blood)
CATABOLISM - mainly in liver

NOTES: Circled numbers are for Identification only.
Sections enclosed by dash lines have not been included in the model.

FIG. 1. Flow Sheet for Adrenocortical System.

experimental conditions both *in vivo* and *in vitro*. The free cholesterol derived from the plasma as well as from small precursors such as acetate is probably the principal source of steroidogenesis while the ester has an indirect role (49). Of the total cholesterol in the adrenal gland, only a portion is considered to be in the free state and the rest is in the form of cholesteryl esters.

2. *Formation of Pregnenolone* (*Reactions 1 and 2*)

At least three enzyme systems, "20α-hydroxylase," "22-hydroxylase," and "C-20, 22 desmolase" take part (26, 93, 95); of these, "20α-hydroxylase" has been studied in greater detail (50). Pregnenolone inhibits the C-20 hydroxylation of cholesterol; the uninhibited rate of *in vitro* hydroxylation was twice the maximally inhibited rate (56). This product feedback inhibition, one of the regulating mechanisms in the biosynthesis of cortisol, has been taken into consideration.

Lipoid Adrenal Hyperplasia: An enzymic defect in the formation of pregnenolone prevents the biosynthesis of adrenocortical and gonadal hormones. In the genetic male, the clinical picture is that of a normotensive male pseudohermaphrodite with cryptorchidism, salt-wasting, low secretion rates of cortisol and aldosterone, and absence of 3β-hydroxy-Δ^5 steroids with either 19 or 21 carbons. The finding of low rather than absent titers of urinary neutral 17-ketosteroids in one patient led to the suggestion that an alternate pathway from cholesterol to dehydroepiandrosterone might exist without the formation of C-21 compounds. In the genetic female with normal female genitalia, the diagnosis can only be suspected (52, 53).

The adrenal glands contain excessive quantities of foam-filled cells containing cholesterol. To date, only a few of the cases reported have survived owing to severe salt loss resulting from a lack of mineralocorticoids and the deficiency in cortisol production (70, 79, 80). A C-20, 22 desmolase defect has been postulated (79) but other defects are also possible, such as one involving cholesterol 20-hydroxylase (24, 52, 53) or a partial defect in the formation of pregnenolone from cholesterol (16).

3. Oxidation of Pregnenolone to Progesterone (Reaction 3)

This step in the biosynthesis of steroid hormones is mediated by "3β-hydroxysteroid dehydrogenase" and "Δ^5-3-ketoisomerase"; the irreversible step catalyzed by the latter enzyme probably determines the rate of overall conversion (59, 83, 98).

The fetal adrenals have a reduced 3β-hydroxysteroid-dehydrogenase activity leading to a secretion of Δ^5-3β-hydroxysteroids (29, 43). In the adrenal neocortex in both sexes the activity appears in the beginning of the fourth month, although Niemi and Baillie have detected it as early as the eighth week of fetal life (44, 67). With the involution of the fetal zone of the adrenal cortex during the first few weeks of life the plasma levels and urinary excretion of Δ^5-3β-hydroxysteroids rapidly fall to very low levels in the infant.

3β-Hydroxysteroid Dehydrogenase Defect: Deficiency of this enzyme affects the biosynthesis of cortisol and aldosterone (9, 10); as a consequence, a severe salt-losing syndrome and Addisonian crisis develops and death often ensues (106). Since the same genetic defect restricts the biosynthesis of testosterone in the Leydig cells of the testes, the differentiation of external genital organs is also disturbed in the male, leading to "male pseudohermaphroditism" or hypospadias. In the female, at birth, the external genitals may be completely unaffected or less virilized than may occur if the enzymic defect restricts the biosynthesis of cortisol at a later stage of the pathway. This presumably results from hypersecretion of a weak androgen such as dehydroepiandrosterone.

Histochemical studies of some affected infants indicate that the 3β-hydroxysteroid dehydrogenase activity in the adrenal is about $\frac{1}{100}$ as compared to the normal infants; the activity of "11β-hydroxylase" was about ⅕ and that of "C-21 hydroxylase" about the same when compared with the normal individuals (12). Excreted urinary metabolites indicate that the defect in these cases is primarily due to the deficiency of 3β-OH-dehydrogenase (11). It is of note, however, that in the older child pregnanetriol may also be found presumably due to the presence of 3β-OH-dehydrogenase in the liver (13) and it has been suggested that 3β-OH-dehydrogenase is also present in the prepubertal testes (71). Nonetheless, the ratio of Δ^5-pregnenetriol to pregnanetriol is always considerably below 1.0 in the "C-21 hydroxylase" deficiency syndrome and always greater than 1.0 in the 3β-hydroxysteroid dehydrogenase disorder (13).

4. *Hydroxylation of Progesterone*

A total of three hydroxyl groups at positions 11, 17 and 21 are required for the conversion of progesterone to cortisol. Although the exact sequence may be debatable and progesterone can be hydroxylated at all three positions, it seems that the preferred sequence is initial hydroxylation at C-17, then at 21, and finally at 11.

A. 17α-Hydroxylase (Reaction 4): Hydroxylation at C-17 has been studied in the adrenal, ovary, and testis (47, 97, 63). A defect in 17α-hydroxylation would limit the biosynthesis of cortisol but not of corticosterone, deoxycorticosterone and aldosterone. An increased ACTH secretion due to cortisol deficiency would lead to increased corticosterone and deoxycorticosterone concentration in the adrenal as well as in the blood and the symptoms of primary aldosteronism. However, aldosterone may not be present in excess because the salt-retaining effect of deoxycorticosterone may suppress aldosterone production via the renin mechanism.

17α-Hydroxylase Defect: Since the biosyntheses of androgens and estrogens also require a prior hydroxylation at C-17 of the C-21 precursors, a genetic anomaly in the ovary may affect the development of female secondary sex characteristics which are estrogen dependent. The clinical picture in the female is of hypokalemia, hypertension, and, at puberty, amenorrhea and lack of 2° sexual characteristics (4, 22, 45, 64).

Large amounts of the tetrahydro derivatives of deoxycorticosterone and corticosterone are found in the urine, but urinary aldosterone, pregnanetriol and neutral 17-ketosteroids, and plasma and urinary cortisol are ordinarily absent or markedly reduced (6). In one instance of the syndrome the clinical picture was of male pseudohermaphroditism with ambiguous genitalia, absence of male secondary sexual characteristics, and gynecomastia occurring at puberty. Plasma testosterone was low (66).

B. C-21 Hydroxylation: Hydroxylation of progesterone, 17α-hydroxyprogesterone, pregnenolone, and 17α-hydroxypregnenolone by a partially purified enzyme preparation has been studied. Although progesterone competitively inhibited the hydroxylation of 17α-hydroxyprogesterone and *vice versa*, suggesting that the same enzyme probably hydroxylates the two substrates, the kinetic parameters were significantly different on a comparative basis (86).

C-21 Hydroxylation Defect: Considering the biosynthesis of cortisol only, a deficiency of 'C-21 hydroxylase' will result in a larger concentration of 17α-hydroxyprogesterone in the adrenal and an excessive secretion into the blood. Normally the concentration of 17α-hydroxyprogesterone in the adrenal is about 4 μg per gm of the tissue, but in two cases with the genetic defect of C-21 hydroxylation the concentration of this intermediate was as high as 160 μg/gm (8, 108).

The daily secretion of 17α-hydroxyprogesterone was estimated to be 240–280 mg per day in a patient with "C-21 hydroxylase" deficiency, as compared to a secretory rate of 3 mg per day in normals (36). Similar findings were reported in two other subjects where production rates of 55 and 113 mg per 24 hours were noted in contrast to production rates of 1.8 mg/24 h in normal subjects (96).

In five untreated patients with congenital adrenal hyperplasia plasma 17-OH-progesterone ranged from 4–22 μg/100 ml and plasma progesterone from 0.2 to 1.1 μg/100 ml (96).

The secreted 17α-hydroxyprogesterone is metabolized and excreted in the urine mainly as pregnane-3α, 17α, 20α-triol. In a male patient with a serious but not complete block, the excretion of this metabolite was 65 mg per day as compared to a normal excretion of 1-2 mg per day (36). Excretion of 11-ketopregnane-3α, 17α, 20α-triol was 12 mg per day as compared to a minimal amount in normals.

Since 17α-hydroxyprogesterone is the immediate precursor of androst-4-ene-3,17-dione also, a block of C-21 hydroxylation diverts an increased amount of the C-21 precursor towards the formation of this adrenal androgen. Androst-4-ene-3,17-dione is hydroxylated at 11β-position (89) and the hydroxylated product is secreted in the blood. As compared to a secretion of about 1 mg per day in normal men and less than this amount in normal women, the secretion of 11β-hydroxyandrost-4-ene-3,17-dione was at least 16 mg per day in a patient with "C-21 hydroxylase" deficiency. Thus, despite the deficiency of "C-21 hydroxylase" in this and similar cases, "11β-hydroxylase" was evidently present in the adrenal cortex (37).

Biosynthesis of aldosterone also requires C-21 hydroxylation; however, in this case the substrate is progesterone instead of 17α-hydroxyprogesterone. Therefore, three types of "C-21 hydroxylase" deficiency cases are possible.

1. When only the biosynthesis of cortisol is affected due to a block in the conversion of 17α-hydroxyprogesterone to 11-deoxycortisol.
2. When only the biosynthesis of aldosterone is affected due to a block in the conversion of progesterone to 11-deoxycorticosterone.
3. When the biosynthesis of cortisol as well as that of aldosterone is affected due to a block in the C-21 hydroxylation of both progesterone and 17α-hydroxyprogesterone.

In the first situation, water and electrolyte balance will not be disturbed; while in the second and third, lack of aldosterone will lead to a disturbance in electrolyte balance. It may be noted that the second case would not be distinguishable clinically from cases with defects in aldosterone biosynthesis due to a lack of C-18 hydroxylation of corticosterone or a subsequent step in the biosynthetic chain. In these latter instances the ACTH level should not rise since it is coupled with the production of cortisol which, presumably, is not affected.

As expected, there are two variants of "C-21 hydroxylase defect", viz., the nonsalt-losing type (1, 23) and the salt-losing type (15, 39, 57). Recent studies have indicated that in children having C-21 hydroxylation defect accompanied by salt loss, aldosterone secretion is low 2-78 μg (mean 21 μg) per 24 hours as compared to a secretion of 26-198 μg (mean 104 μg) per 24 hours in normals (15). On the other hand, a group of five nonsalt wasters with congenital adrenocortical hyperplasia had aldosterone secretory rates of 344.1 ± 76.3 μg/24 h as contrasted to normal values of 94.0 ± 31.4. On salt depletion the values in the former group rose to 1099 ± 350 μg/24 h (21). Three hypotheses have been forwarded to explain the difference between salt losers and nonsalt losers with a C-21 hydroxylation defect:

(A) Salt loss, to a large extent, is a consequence of a secretion of an active salt-losing hormone by the adrenal gland (54). Although such a hormone has eluded attempts for its isolation and identification, it is known that progesterone and 17α-hydroxyprogesterone have physiologic activity antagonistic to that of aldosterone at renal tubules. Both of these intermediates are likely to be secreted in excessive amounts in the event of C-21 hydroxylation block (36); this would lead to an apparent deficiency of aldosterone activity although its production may not have been impaired. However, since aldosterone production is impaired (15), this explanation alone appears to be insufficient. It is probably due to an overproduction of these intermediates and a decreased ability to synthesize aldosterone (39, 57).

(B) A more severe defect of C-21 hydroxylation will affect the biosynthesis not only of cortisol but also of aldosterone (39). This explanation suggests that the same enzyme is involved in the hydroxylation of progesterone and 17α-hydroxyprogesterone. The relative rates of hydroxylation will largely depend on V_{max}/Km of progesterone compared to that of 17α-hydroxyprogesterone at low substrate concentrations. On a comparative basis for progesterone and for 17α-hydroxyprogesterone, V_{max}/Km are .67 and .98 respectively, suggesting that with comparable substrate concentration hydroxylation of the latter substrate proceeds at a faster rate. However, in case of a partial "C-21 hydroxylase" deficiency the activity of "17α-hydroxylase" will determine the amount of progesterone and 17α-hydroxyprogesterone available for the enzyme system, and this in turn will determine the amount of aldosterone and cortisol production. (See Table VII and Figure 11a)

(C) Another explanation which is in keeping with the hypothesis that the same enzyme is involved in the hydroxylation of progesterone and 17α-hydroxyprogesterone has been provided by Visser (102). The genetic defect in case of salt losers is visualized at DNA, at a site leading to a different change in the amino acid sequence of the "C-21 hydroxylase," as compared to an analogous change in nonsalt losers. (See Table VI)

In salt-losing cases, the formation of enzyme-substrate complex with progesterone as well as 17α-hydroxyprogesterone is affected; while in the nonsalt-losing cases only the association of the latter substrate is affected. This hypothesis can explain the wide variation observed in the degree of C-21 hydroxylation defect suggested above.

Bartter et al (1) also believe that the two syndromes are genetically distinct from each other. However, they suggest that probably two separate isozymes of 21-hydroxylase for C-21 steroids exist.

C. 11β-Hydroxylation: Usually the substrates for this "enzyme system" are 11-deoxycorticosterone, 11-deoxycortisol, and androst-4-ene-3,17-dione. Adrenal androgens, particularly androst-4-ene-3,17-dione, appear to be competitive inhibitors for the hydroxylation of DOC as well as 11-deoxycortisol (88, 89).

11β-Hydroxylation Defect: Cases of genetic defect of this step in the biosynthesis of cortisol have been observed in children (31) as well as in females after puberty (28, 40). The disturbance leads not only to the androgenic manifestations, i.e., virilization and rapid somatic advance, but also to a characteristic vascular hypertension (30) which may be the result of the production of excessive amounts of 11-deoxycorticosterone. However, some cases without hypertension have also been reported (3, 18, 42, 92, 107).

A decreased biosynthesis of aldosterone is also expected as a result of the limitation on the formation of corticosterone from 11-deoxycorticosterone (79, 92). Patients with 11-hydroxylation defects were found to be excreting increased amounts of tetrahydro-11-deoxycortisol, tetrahydro-11-deoxycorticosterone and 11-deoxy-17-ketosteroids (31, 40).

5. C-18 Hydroxylation

Hydroxylation at C-18 and subsequent dehydrogenation appears to be required in the proposed schemes for aldosterone biosynthesis (85). Conversion of corticosterone to 18-hydroxycorticosterone and aldosterone has been studied in some detail. Experimental data on 18-ol-dehydrogenation is meager, probably because of limited availability of the substrates and the difficulty in separating "18-ol-dehydrogenase" from "C-18 hydroxylase" (81).

Defect of C-18 Oxidation: Genetic defect of C-18 oxidation of corticosterone severely limiting aldosterone biosynthesis has been reported (103). Whether the defect was in the conversion of corticosterone to 18-hydroxycorticosterone or that of the latter to aldosterone was not ascertained. The patients showed severe salt loss, but there was no increase in the secretion of adrenal androgens in response to ACTH administration; the cortisol secretion was increased as expected, but aldosterone secretion did not change despite increased secretion, hence the biosynthesis of the precursor corticosterone. The patient was not virilized and the adrenals had the normal weight and appearance; urinary excretion of 17-ketogenic steroids and 17-hydroxycorticoids was within the normal range.

Genetic defect of "18-ol-dehydrogenase" has also been observed (99). On a high (148 mEq/48 h) sodium intake, aldosterone secretion was 10.9 μg per day (54.5 μg/d/m^2 surface area) and the secretion of 18-hydroxycorticosterone was 1.6 mg/d. Normal range for aldosterone secretion is reported to be 40-130 μg/day/m^2 in adults (100); the secretion of 18-hydroxycorticosterone is considered to be two to three times this value in adults (101). A normal (14 mEq/48 h) sodium intake increased the daily secretion of 18-hydroxycorticosterone to 2.4 mg/d, but the aldosterone secretion was only 8.3 μg/day (40 μg/d/m^2).

* * *

The above mentioned studies indicate the complexity of the adrenocortical system. It is presumed that the ultimate objective of *in vivo* and *in vitro* studies is the extrapolation of the findings to the human body for a better understanding of the system under physiologic as well as various pathologic conditions. However, experimental studies, despite the ingenuity of the worker, often face serious limitations. In addition to the well-recognized constraints imposed by the choice of the subjects, their positions on the temporal course of development, the choice of the time domain selected for the study, the large number of state variables, and their nonlinear responses to the experimental conditions (inputs) severely limit the amount of information that can be obtained from any one experiment. Changes in some of the state variables may be observable, but technical difficulties often make measurement impractical. Also, it is difficult if not impossible to observe the time course of a particular variable for an extended period without disturbing the rest of the system. The limitations of chemical analysis combined with the need for sequential sampling without disrupting the rest of the system make irreconcilable demands on the experimental investigation of certain phases of the adrenocortical system.

The development of a mathematical model on the basis of available information is an alternative to direct experimentation. This is necessarily an approximation procedure since the functional significance of the various components are only partially known and their interrelations are incompletely understood. Also, only a few of the kinetic parameters of the enzymic reactions have been studied. The mathematical construct described below attempts to incorporate the quantitative information available from experimental studies in this and other laboratories.

Digital Computer Model of the Adrenocortical Hormone System

The digital computer model is a numerical representation of the adrenocortical system. The usefulness of such a model is measured by two important properties:

1. The accuracy of the results—the degree to which they match the observed behavior of the original system—and
2. Its rationality—the degree to which the structure of the model matches the structure of the original system.

This second property, while not quite as important as the first, is vital for the clinical or laboratory uses of the model. In the model described here, the form and structure are derived directly from biochemical descriptions of the adrenocortical system (Fig. 1), and all of the parameters used in the model have direct biochemical significance.

One of the most interesting characteristics of this system is its behavior as a feedback control system to regulate the levels of various body chemicals. However, the temptation to structure the model like a classic feedback control system has been resisted, since examination of the probable biochemical mechanisms shows that the control is accomplished by means of parametric coupling—the concentration of one chemical affecting the production of another through inhibition or stimulation, a nonlinear phenomenon.

Numerical Formulation

The computation of the time response of the model is based on a time interval short enough so that none of the production rates change by a significant amount during that time. The general order of computation (Fig. 2)

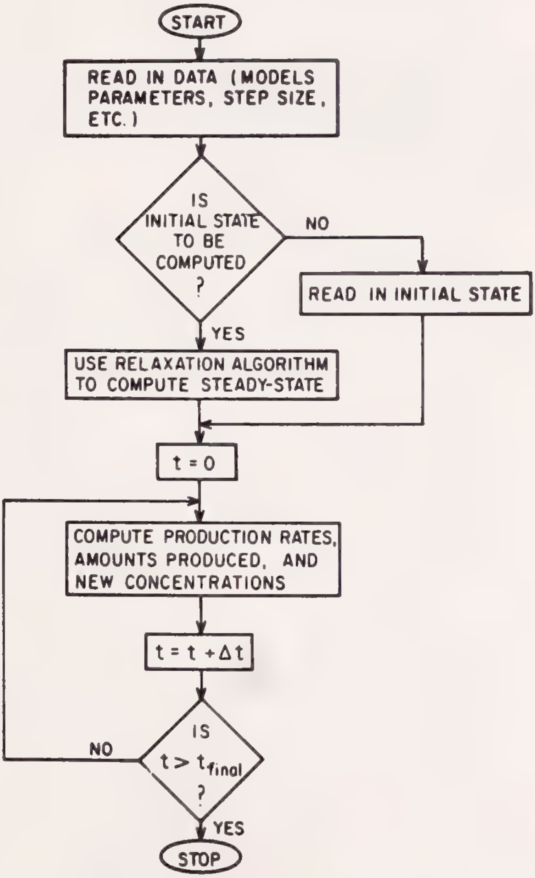

START
READ IN DATA (MODELS PARAMETERS, STEP SIZE, ETC.)
IS INITIAL STATE TO BE COMPUTED ?
NO
READ IN INITIAL STATE
YES
USE RELAXATION ALGORITHM TO COMPUTE STEADY-STATE
t = 0
COMPUTE PRODUCTION RATES, AMOUNTS PRODUCED, AND NEW CONCENTRATIONS
t = t + Δt
NO
IS t > t_final ?
YES
STOP

FIG. 2. Flow Chart of Overall Program Operation.

is first to compute the production rate based on the values of the state variables (substrate concentrations) at the beginning of the time interval, next to compute the amount of chemical produced in the time interval, and then to update the concentration. The process is then repeated for all of the chemical substances. This method is essentially Euler's method for integrating ordinary differential equations (94) and bases the integration over each time step entirely on values of the substrate concentrations at the beginning of the step. Other methods offer advantages in maximum allowable step size for a given accuracy, but Euler's method is by far the easiest to program and to use. If computing costs do not become excessive, there seems to be no advantage in using any of the more complex methods. A further point to note is that the maximum step size that can be used is limited by the speed of the fastest reaction in the system, regardless of the speed of any of the others or other accuracy considerations.

Each reaction is governed by the biosynthetic rate equation, reproduced below for the case of a substrate A forming a product B:

$$(dB/dt)_{\mathrm{prod}} = V_{\mathrm{max}}a/(a + K_m)$$

Where lower case letters refer to concentrations, capital letters refer to actual quantities present, and no inhibitors or stimulants are present. The subscript "prod" indicates that this is the change in B due only to production. For the purposes of numerical computation, the production rate is assumed to be constant over a small time increment, Δt, and the quantity of B produced during the time period is

$$\Delta B_{\mathrm{prod}} = (V_{\mathrm{max}}a/(a + K_m))\Delta t$$

The amount of B lost is described by a similar relation (for example, B reacting to produce C) and the *net* change in B is then computed. Any number of sources or destructive paths can be considered in the same manner. After the total quantity of B present has been updated to include the change over the time increment, a new value of concentration is computed by dividing the quantity by the pool volume (a separate pool volume is used for each substance to account for different fluid volumes in various compartments). The basic biosynthetic rate equation is nonlinear (because of the substrate concentration in the denominator) even before consideration of inhibitors or stimulants. At "normal" operating levels, however, K_m is much greater than the substrate concentrations permitting some of the equations to be linearized. Since this has the effect of suppressing the saturating characteristics of the reactions, which often appear in clinical conditions or in case of infusions or injections of large quantities of ACTH, linearization is not recommended. For reactions whose rates are modulated by inhibitors or stimulants, the appropriate forms of the biosynthetic rate equation are

$$(dB/dt)_{\mathrm{prod}} = V_{\mathrm{max}}a/(a + K_m)\,(1 + j/K_j)$$

for noncompetitive inhibition by the species J, where j is the concentration of J, K_j is the inhibition constant, and a is the substrate concentration. For competitive inhibition, the rate equation is

$$(dB/dt)_{\mathrm{prod}} = V_{\max}a/(a + K_m(1 + kK_{\mathrm{K}}))$$

where k is the concentration of the competitive inhibitor K and K_{K} is the inhibition constant. The more general forms of these equations are written for partially competitive or partially noncompetitive reaction rate modulation and can account for inhibition or stimulation. For partially noncompetitive modulation the rate equation is:

$$(dB/dt)_{\mathrm{prod}} = V_{\max}a(1 + Rj/Kj)/(a + K_m)(1 + j/K_j)$$

The parameter R controls the nature of the modulation: if R is greater than one the substance J will stimulate the reaction, if R is less than one it will inhibit the reaction, and if R is equal to one the concentration of J will have no effect on the reaction. If R is equal to zero, the equation reduces to the case of pure noncompetitive inhibition, given above. A similar equation exists for partial competitive modulation. In the computational model the production rates are again approximated by averages over a small time increment; the concentrations of the modulating substances at the start of the time period are used to compute the production rate for that time period.

Hormones produced in the adrenal get into the blood by diffusion. In order to accurately represent the system dynamics it is necessary to designate state variables (quantities which fix the dynamic state of the system at any instant) for the concentrations within the adrenal and for the concentrations in the blood. For the purposes of this study, the diffusion rates were assumed to be proportional to the differences in concentration from the adrenal to the blood. Where possible, the diffusion rate coefficients were chosen on the basis of experimentally determined secretion rates. In order to account for the blood transport time, a time delay of two minutes was introduced between the secretion of cortisol into the blood and its appearance at the hypothalamus or pituitary.

The binding phenomenon has a strong effect on the dynamic response of hormone systems. In this system, the binding of cortisol to transcortin is the most significant binding reaction since cortisol is the main element in the feedback regulating loop to ACTH. For the sake of simplicity, other binding reactions were not included. The rate at which a hormone A is bound to B (or unbound) is given by

$$(dA/dt_{\mathrm{binding}} \quad k_1(a \cdot b) - k_2a$$

where, again, lower case letters represent concentrations and capitals represent total quantities present. Note that in this case the reaction can go either way—the production rate can be either positive or negative—depending on the relative magnitudes of the two terms in the rate equation. Separate state variables must be defined for free A, free B, and for the bound compound. For numerical analysis, the equation is treated exactly like the biosynthetic rate equations.

The scheme of computation, then, consists of the approximate integration of a set of differential equations, using one first-order equation for each state variable (or identifiable quantity). For the adrenocortical system this amounts to about thirty differential equations, each of which requires an initial condition (concentration at $t = 0$) to start the computation. A stable equilibrium state is the most logical starting point for dynamic studies; this is a state for which all concentrations are constant with time, and thus for each substance, the net production rate must equal the net destruction rate. By equating production rates and destruction rates, a set of nonlinear algebraic equations is generated whose solution gives the desired steady-state condition. An iterative, relaxation type solution is used to compute the steady-state condition and thus the initial state for the dynamic solution. The iterative solution converges very rapidly for most cases, but with some combinations of parameter values it does not converge at all. When this occurs, an alternative method for generating the starting conditions is to give the system zero initial states on all the state variables, and then simply to permit the dynamic solution to run for a long enough period of time so that transients die out.

Parameter Determination

This model, with approximately thirty different equations, contains about 75 independent parameters which must be fixed in order to compute a time response. One property of a numerical simulation model is that no "unknown" or "undetermined" parameters can exist: since the computation is numerical, values must be found, in one way or another, for every parameter before any results can be produced. The major parameters are the $V_{\max}$'s and K_m's for each reaction, the inhibition and stimulation constants, and the diffusion rate coefficients. The values and units for all of the parameters used in the stimulation are shown in Tables I and II. As a start, whenever experimentally determined values were indicated in the literature, these were used in the model. The parameters for which no reliable values could be found were estimated to obtain a complete preliminary working model. If all or nearly all of the model parameters could be fixed by employing experimental or theoretical values, obtained from the literature, the model for the normal system could be tested at this point by comparing its predicted response to a series of disturbances with the observed response of the actual system to the same disturbances. In this case, however, not nearly enough data were available, so remaining parameters were determined through the parameter identification process below.

The problematic nature of parameter determination raises an important question in the philosophy of modeling: to what degree can a model with so many arbitrarily fixed parameters be significant? In an absolute sense a model is no better than our knowledge of each of the parts that make up the model. One can never have complete confidence in a model anymore than one can ever obtain exact solutions to any problems involving physical systems; judgment must therefore be used in determining the ranges of validity a model is likely to have and the amount of confidence that should be placed on the

TABLE I

V_{max} and K_m Values Used in the Model

Reaction No.	V_{max} M/min	K_m M/l	Reaction No.	V_{max} M/min	K_m M/l
1	4.3×10^{-8}	$.57 \times 10^{-5}$	17	$.2 \times 10^{-3}$	$.74 \times 10^{-4}$
2	$0.6 \times 10^{\text{[illegible]}}$	$.54 \times 10^{-5}$	18	.15	—
3	1.1×10^{-4}	1.7×10^{-4}	19	$.56 \times 10^{-4}$	$.74 \times 10^{-4}$
4	$.65 \times 10^{-5}$	$.74 \times 10^{-4}$	20	$.25 \times 10^{-2}$	—
5	2.94×10^{-6}	3.03×10^{-5}	21	$.124 \times 10^{-4}$	$.74 \times 10^{-4}$
6	$.15 \times 10^{\text{[illegible]}}$	$.6 \times 10^{-4}$	22	$.4 \times 10^{-6}$	$.6 \times 10^{-4}$
7	2.5×10^{-7}	2.08×10^{-5}	23	$.3 \times 10^{-6}$	$.85 \times 10^{\text{[illegible]}}$
8	$.17 \times 10^{-4}$	$.74 \times 10^{-4}$	24	.3	—
9	$.6 \times 10^{-4}$	$.74 \times 10^{-4}$	25	$.2 \times 10^{-8}$	$.8 \times 10^{-7}$
10	$.2 \times 10^{-3}$	$.74 \times 10^{-4}$	26	$.153 \times 10^{-4}$	$.74 \times 10^{-4}$
11	.020	—	27	$.9 \times 10^{-6}$	$.74 \times 10^{-4}$
12	$.1 \times 10^{-4}$	—	28	$.78 \times 10^{-6}$	$.19 \times 10^{-4}$
13	$.8 \times 10^{-4}$	$.74 \times 10^{-4}$	29	.12E-3	—
14	$.5 \times 10^{-2}$	—	30	.436E-5	$.74 \times 10^{-4}$
15	$.12 \times 10^{-3}$	$.74 \times 10^{-4}$			
16	$.25 \times 10^{-1}$	$.3 \times 10^{-4}$			

TABLE II

Inhibition/Stimulation Modulation Coefficients (Normal Case)

Reaction Affected	Symbol (See Fig. 1)	Value
1	KAC	3.8 m un/l
1	RAC	10.0
1	KPR	0.15×10^{-6} M/l
7	KAD	0.5×10^{-4} M/l
13	KCOR	0.5×10^{-9} M/l
13	KAB	0.947 m un/l
8	KCO	0.25×10^{-7} M/l

predictions it makes. In order to insure a level of significance beyond that of pure curve fitting, the structure of the adrenocortical system model (i.e., the chemical flow diagram for the system) and the forms of the rate equations were entirely fixed from biochemically supported hypotheses. These put very strong constraints on the nature of responses that could be obtained from the model, regardless of the choice of parameter values. Further quantitative discussion of the effects of parameter variation on the responses is given in the section on parameter sensitivity.

Experimentally obtained information pertaining to the adrenocortical system performance was used as the primary input for parameter identification. This information was primarily steady-state in nature, concentrations, secretion rates, half-lives, etc., so that the major goal of the identification was to match the steady-state equilibrium state of the model to all known measurements. Excellent agreement was obtained (see Table III, a to d); the only significant exception, the aldosterone, occurred because a known binding

TABLE IIIa

Secretory Rate of Certain Adrenal Steroids

Compound	Moles per 24 hrs
Progesterone	$1.4–2.8 \times 10^{-6}$
17α-hydroxyprogesterone	$\sim 9.6 \times 10^{-6}$
11-deoxycorticosterone	$1.2–1.8 \times 10^{-6}$
after metyrapone administration	125-fold increase
Corticosterone	$5.8–14.5 \times 10^{-6}$
Cortisol	$41.7–83.6 \times 10^{-6}$
Aldosterone	
(8–18 yrs)	$0.24–5.5 \times 10^{-6}$
(18–35 yrs)	$\sim 0.21 \times 10^{-6}$
(67–88 yrs)	$\sim 0.10 \times 10^{-6}$
(all ages)	Av. 0.25×10^{-6}
On salt deprivation	$0.50–.75 \times 10^{-6}$
	(Av 2- to 3-fold increase)
Aldosterone	
In CAH—non-salt losers	
On normal Na⁺ intake	$.31–4.7 \times 10^{-6}$
On restricted Na⁺ intake	$.71–9.0 \times 10^{-6}$
In CAH—salt losers	
On normal Na⁺ intake	$< .02 \times 10^{-6}$
On restricted Na⁺ intake	No change
In CAH—before corticoid suppression	$.31–.48 \times 10^{-6}$
after corticoid suppression	$.13–.21 \times 10^{-6}$
Restricted Na⁺ intake—normal	2.0×10^{-6}
after maximum ACTH stimulation	6.2×10^{-6}
On salt loading diet—normal	0.28×10^{-6}
after maximum ACTH stimulation	1.5×10^{-6}
Production rate of androgens	
Androst-4-ene-3,17-dione	
Normal young	
males	5.0×10^{-6}
females	11.8×10^{-6}
Testosterone	
Normal young	
males	$20.8–27.1 \times 10^{-6}$
females	$1.3–6.8 \times 10^{-6}$
Children	
normal	$< 1.7 \times 10^{-6}$
with CAH	$1.2–39.1 \times 10^{-6}$
11β-Hydroxyandrost-4-ene-3,17-dione	
normal	$< 3.0 \times 10^{-6}$
with CAH (C-21 hydroxylation defect)	$18.0–53.0 \times 10^{-6}$
Dehydroepiandrosterone	$52.0–104.0 \times 10^{-6}$

was not included in the model. Unfortunately, there is not enough data available to fix all of the model parameters. One particular problem is that in the normal state the reactions are operating well below their saturation levels. Thus only the ratio $V_{\max}/K_m$ is important in determining production rates, because the value of K_m is much larger than the substrate concentration value.

TABLE IIIb

Average Concentration of Certain Steroids in the Blood Plasma Determined by Chemical Analyses

Compound	Concentration Moles per Liter
Progesterone	
Men	0.9×10^{-9}
Women	
follicular phase	4.4×10^{-9}
luteal phase	50.8×10^{-9}
ovariectomized	1.2×10^{-9}
ovariectomized and adrenalectomized	0.3×10^{-9}
17α-hydroxyprogesterone	
Men	2.9×10^{-9}
Women	
follicular phase	1.3×10^{-9}
luteal phase	5.3×10^{-9}
11-deoxycortisol	
Adult	6.7×10^{-8}
after blocking 11β-hydroxylation by metyrapone infusion	35.0×10^{-8}
Corticosterone	
Adult	4.4×10^{-8}
after ACTH stimulation (IV 25U/8 hrs)	$21.9\text{–}29.2 \times 10^{-8}$
Cortisol	
Adult	
morning	4.5×10^{-7}
4 P.M.	2.2×10^{-7}
midnight	1.4×10^{-7}
Effect of ACTH administration:	
Adults before ACTH	$2.2\text{–}6.7 \times 10^{-7}$
after maximum stimulation by 25U/6 hrs. IV or 40U every 2 hrs. intramuscular	$8.9\text{–}15.0 \times 10^{-7}$
Children (4–11 yrs.)	
before ACTH	1.9×10^{-7}
after 5U/1 hr. IV	7.6×10^{-7}
Adult	
in clinical shock	up to 16.6×10^{-7}
6 hrs. after surgery (highest levels)	$12.4\text{–}19.3 \times 10^{-7}$
Adult	
Cushing's syndrome	$9.2\text{–}11.7 \times 10^{-7}$
Adrenocortical carcinoma	$15.3\text{–}19.7 \times 10^{-7}$
Adult	
Dexamethasone administration 1 mg/hr. IV	Prompt exponential fall
after 3 hours	About 25% of the initial value
Aldosterone	
Males	
young	1.3×10^{-10}
elderly	0.7×10^{-10}
Adult	
Cushing's syndrome:	
Adrenal hyperplasia	2.8×10^{-10}

TABLE IIIb—*Continued*

Compound	Concentration Moles per Liter
Adenoma	3.3×10^{-10}
Addison's disease	$<0.2 \times 10^{-10}$
Primary aldosteronism	
before surgery	$6.6–33.0 \times 10^{-10}$
after surgery	$0.8–3.3 \times 10^{-10}$
Congenital adrenal hyperplasia	1.7×10^{-10}
Androst-4-ene-3,17-dione	
Adult	
male	$2.1–3.5 \times 10^{-9}$
female	$3.5–10.5 \times 10^{-9}$
Child and adolescent	
male	$\sim 3.0 \times 10^{-9}$
female	$\sim 1.0 \times 10^{-9}$
Congenital adrenal hyperplasia	
males—untreated	$7.7–23.1 \times 10^{-6}$
after suppression by cortisol	$0–2.0 \times 10^{-6}$
females—untreated	$19.2–25.1 \times 10^{-6}$
—after suppression	$0.6–3.2 \times 10^{-6}$
Testosterone	
Adult	
male	$7.0–59.0 \times 10^{-9}$
female	$1.7–3.5 \times 10^{-9}$
Child and adolescent	
male	$\sim 1.4 \times 10^{-9}$
female	$\sim 0.7 \times 10^{-9}$
Congenital adrenal hyperplasia	
males—untreated	$4.2–6.6 \times 10^{-9}$
—after suppression by cortisol	$0.7–2.4 \times 10^{-9}$
females—untreated	$3.8–6.2 \times 10^{-9}$
—after suppression	$0–0.2 \times 10^{-9}$

In all of the studies that follow, the model was used in exactly the form determined by the parameter identification studies; no changes were made except those indicated by hypothesis being examined. The parameter values for the normal model have been summarized in Tables I and II.

A great deal of work remains to be done, both experimentally and analytically, in order to determine all the parameters for this model. The general agreement between simulated and measured steady-state conditions and the results of the dynamic and clinical studies which follow indicate that the model has the potential of becoming a highly accurate representation of the adrenocortical system as more basic parameters become known.

Programming and Computer Considerations

The simulation program is written in Fortran IV and runs on a CDC 6400 computer*. Output is obtained in graphic and tabular form. The cost of

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* University of California, Berkeley, Computing Center.

TABLE IIIc

Average Half-life of Certain Compounds in Blood Circulation Calculated from Experimental Data

Compound	Half-life, Minutes
Progesterone	5 and 25–30
Corticosterone	~70
11-Deoxycortisol	23–71
Cortisol	
normal	75–120 (Av. 92)
during 3rd trimester of pregnancy	140
during laparotomy	170
in liver disease	up to 420
Dexamethasone	200
Aldosterone	Av. 34
ACTH	3–5

TABLE IIId

Secretion Rates, Concentrations in the Blood Plasma, and Half-Lives for the Normal State Values from the Stimulation Model

Compound	Secretion Rate (Moles per 24 hr.)	Concentration in the Blood Plasma (Moles per liter)	Half-Life (min.)
Progesterone	3.32×10^{-6}	1.39×10^{-9}	25
17α-hydroxyprogesterone	2.0×10^{-5}	5.15×10^{-9}	1.5
11-deoxycorticosterone	0.971×10^{-6}	—	71
Corticosterone	8.2×10^{-6}	—	—
Cortisol	76.3×10^{-6}	5.62×10^{-7}	70
Aldosterone	0.55×10^{-6}	18.7×10^{-10}	20
Androgen—Δ^4-Dione	6.85×10^{-6}	3.55×10^{-9}	2.6
ACTH	3.5 IU per day	3.0 m un per liter	5

obtaining information from a simulation program is related most directly to its computer running time characteristics; this program requires approximately twenty seconds of computer time to simulate one hour of system time. The amount of computer time required for the simulation of other biochemical systems similar in nature to the adrenocortical system will scale linearly with the number of state variables.

Simulation of Experimental and Clinical Studies

The utility of a model can only be assessed with reference to a larger context. The adrenocortical system is described by certain observable physical and chemical quantities and their interrelations. Its analog consists of certain mathematical functions and the variables contained therein. If a model were developed to reproduce the behavior of the adrenal cortex based only on two variables—the input and the output—within specified limits, its degree of isomorphism with the prototype would be low. For certain purposes, such a model (105) might be quite adequate, particularly if one wished to study other parts of a larger system in which the prototype is only a part. But, because the enzymatic reactions constituting the sequence for the biosynthesis of the corticoids are the determining factors in most cases of clinical disorders of the adrenocortical system, a high degree of isomorphism is desired. These disorders are not rare and their study is of immediate interest.

Consequently, available experimental information on the biosynthetic pathways was given a major consideration in constructing the model presented above. Simulation of certain clinical disorders, based on the hypotheses presented by various investigators, has been attempted in the following section to develop an interaction between the mathematical construct and experimental studies.

Effect of ACTH and Glucocorticoid Administration

The mechanism of ACTH action(s) is debatable, but its effects on the adrenal cortex have been studied in detail. These include stimulation of the biosyntheses of corticosteroids, accelerated phosphate turnover, and a decrease in the cholesterol and ascorbic acid concentrations. Cortisol is the major glucocorticoid secreted by the normal human adrenal cortex. Its secretion under basal conditions as well as in response to stress is dependent upon ACTH.

Infusions of ACTH as low as 0.05 units per hour, IV, increase cortisol secretion (62). The maximum response has been obtained by infusing 0.4 units per hour (60). However, most investigations assure maximum response by administering 25–30 IU infused IV over 4 to 8 hours or 40 IU given intramuscularly per day. Eik-Nes et al observed that IV infusion of 25 IU in 6 hours gave a maximal rate of increase in plasma 17α-hydroxycorticosteroids, although the effect did not seem to be much different when the period of infusion was 4 hours (32).

The effect of maximal stimulation with ACTH in normal subjects and in patients with various diseases has been studied (68). The mean response to ACTH infusion in normals was an increase in plasma concentration of 17α-hydroxycorticosteroids from 7 μg per 100 ml to a range of 32–51 μg per 100 ml; a similar increase has been reported by Nugent and Mayes (69). In response to ACTH there occurs an initial brisk rise in plasma levels to more than twice the resting concentration at 30 min. (61), but cortisol concentration can show a slow rise even as late as 8 hours (17). A maximum production rate of cortisol, 150 mg/day, was found to increase the body pool from 2 mg to 10 mg (75).

Stimulation due to clinical shock in patients undergoing surgery raised the corticoid levels in plasma to 45–70 μg per 100 ml (33, 65). A range of 33–43 μg per 100 ml in Cushing's syndrome (38) and 55–71 μg per 100 ml in adrenocorticol carcinoma (72) have also been reported.

The effect of infusion of dexamethasone and cortisol has been studied by several investigators, including Nugent et al (68) and James et al (51). In the latter study infusion of 1 mg of dexamethasone per hour led to a prompt exponential fall in the plasma cortisol concentration; after 3 hours the concentration was 23–27 per cent of the initial value.

ACTH stimulates the secretion of aldosterone also, but the amount required to increase aldosterone secretion is greater than that required for maximal cortisol secretion. ACTH infusion (25 IU in 8 hours) in 8 to 18-year old normals increased urinary excretion of Porter-Silber chromogens from 4–12 mg to 20–60 mg per day; however, the increase in aldosterone excretion ranged from 5–20 μg to 13–62 μg per day (82). Plasma concentration of aldosterone in young males is usually about 4.7 mμg per 100 ml (35). In Cushing's syndrome due to hyperplasia the concentration rose to about 12 mμg per 100 ml (55).

The rate of aldosterone secretion is not directly affected by the concentration of aldosterone in peripheral blood as in the case of cortisol (7). It is indirectly controlled by the blood volume (2). Also, a potent stimulus for aldosterone secretion is the restriction of sodium chloride intake. Secretion of aldosterone in young normals is about 80 μg per day (35); in Cushing's syndrome due to hyperplasia the secretory rate rose to 100–200 μg per day (55).

Infusing ACTH or increasing its level by blocking cortisol production also has an effect on the secretion of other corticosteroids. Corticosterone concentrations in plasma maintain a constant relationship to those of cortisol throughout 24 hours with a maximum level of about 1.5 μg per 100 ml (73). In normal individuals Brorson (14) reported concentrations of 10.2 μg of unconjugated cortisol and of 1.2 μg per 100 ml of corticosterone. Infusion of 25 IU of ACTH in 8 hours raised the corticosterone levels to a range of 7.5–10.0 μg per 100 ml (74). The blood production rate of corticosterone in normals has been found to be in the range of 0.9–4.4 mg per day (75,5); in Cushing's syndrome the production rate was 9.0 mg per day.

The normal secretion rate of 11-deoxycorticosterone (DOC) is 0.4 to 0.6 mg per day (20). Under the influence of metyrapone, when the adrenal is presumably stimulated maximally, the secretion rate of DOC rose 125 fold (46). Concentration of 11-deoxycortisol in plasma is normally 0–2.3 μg per 100 ml (25, 104). On infusion of metyrapone, the concentration rose to 12 μg per 100 ml, and the secretion rate rose to 230 mg per day (77).

Simulation of ACTH Administration and Suppression of the Adrenal Cortex by Cortisol Infusion

The simulated effects of the infusion and injection of ACTH and of the infusion of cortisol on aldosterone, ACTH, and cortisol blood concentrations are shown in Figures 3 to 6. The major qualitative characteristics of these simulated responses agree with the experimental observations. For large scale infusion of ACTH, the rate of infusion appears to have little effect; the final values and rates of rise for the cortisol and aldosterone concentrations are essentially identical for infusion of 25 IU of ACTH over 2 hours and over 6 hours (Figs. 3 and 4). This is a graphic demonstration of the system's basic nonlinearity, since a linear system would be expected to respond in proportion to the strength of the stimulus. Comparison with the experimental data above shows that the effect of ACTH at maximum stimulation is weaker for the model than has been observed.

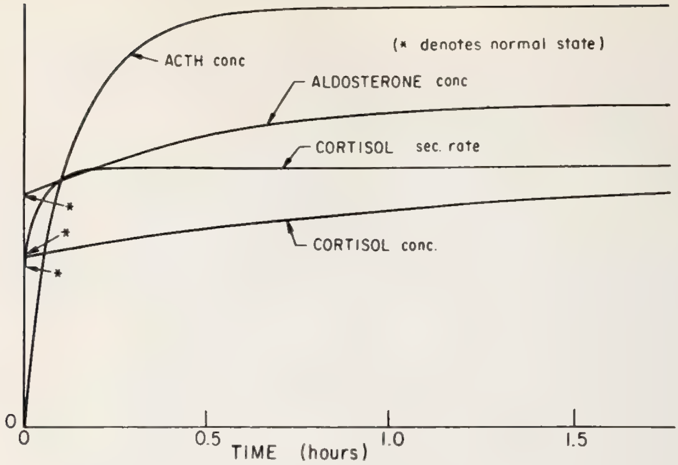

FIG. 3. ACTH Infusion—25 Int'l units in 2 hours.

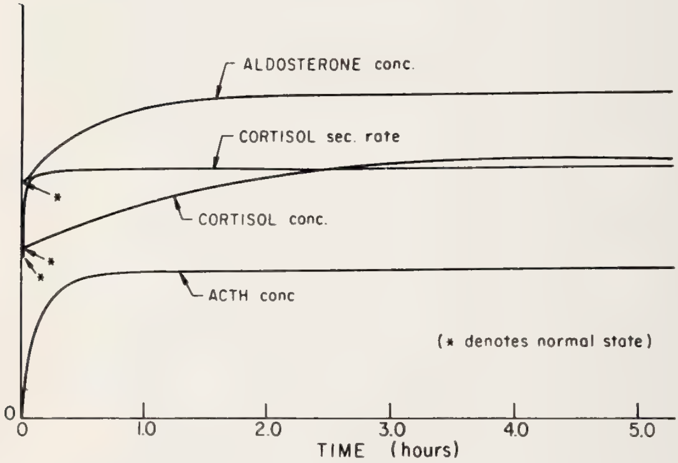

FIG. 4. ACTH Infusion—25 Int'l units infused in 6 hours.

Simulated injection of ACTH is shown in Figure 5. The response again exhibits the nonlinear saturation phenomenon, since the response to a 10 IU injection is only slightly less than the response to a 25 IU injection. ACTH injection, as simulated, has only a limited effect: its half-life is so much shorter than that of cortisol or aldosterone that the added ACTH in the blood decays to a very low concentration before it has a chance to have much effect (note that the total time shown in the figure is only a little more than an hour and a half). Simulation of cortisol infusion (Fig. 6) displays the characteristic fall in ACTH and aldosterone concentrations as the cortisol is administered.

Certain Disorders of the Adrenal Cortex and Their Simulation Studies

In addition to cortisol and aldosterone, the adrenal cortex secretes several other steroids, including "adrenal androgens," corticosterone, and progester-

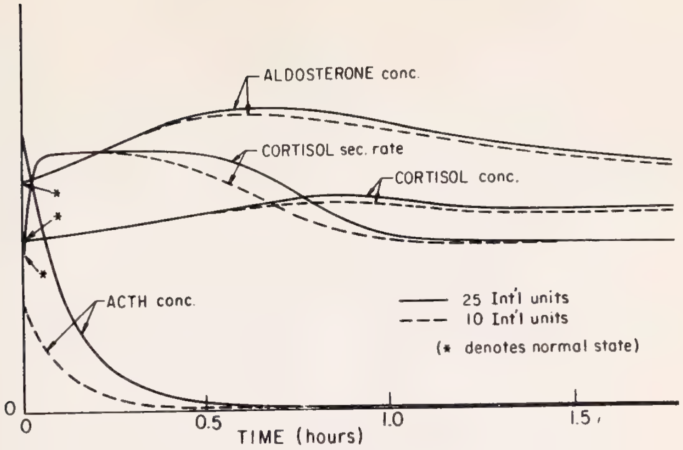

FIG. 5. ACTH Injection.

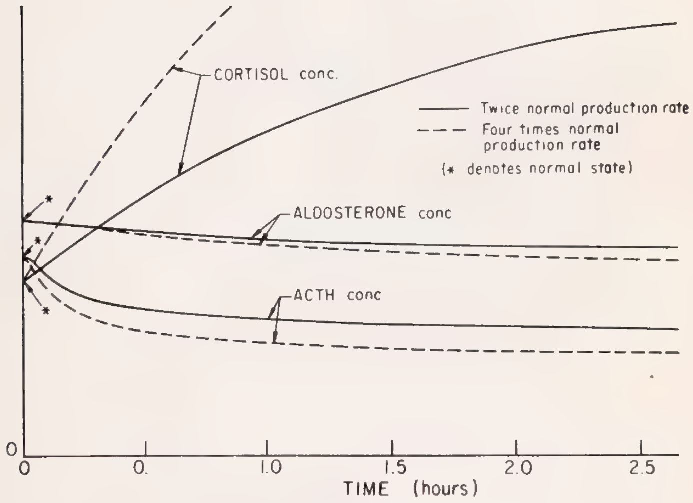

FIG. 6. Cortisol Infusion.

one. Secretion of other steroids such as 17α-hydroxyprogesterone, 11-deoxycorticosterone, and 11-deoxycortisol can be excessive under abnormal circumstances. Secretion of estrogens by the adrenals is not significant except in patients with feminizing tumors of the adrenal cortex (41).

A large number of disorders of the adrenocortical system is a consequence of abnormal secretion of steroids by the adrenals. The primary cause of the disorder may be located either within the adrenal itself or in some other component of the system, e.g., in the hypothalamus or the anterior pituitary. In cases of primary or secondary hyperactivity of the adrenal, the syndrome produced depends upon the rates of secretion of glucocorticoids, mineralocorticoids and the sex hormones. The abnormal secretion of these hormones may be due to a disturbance in the normal sequence of corticosteroid biosynthesis in nontumorous adrenals. Most frequently this impairment is due to a relative deficiency of one of the enzymes necessary for corticosteroid biosynthesis. This congenital defect is caused by a recessive autosomal gene for which clinical manifestations appear in the homozygous state. The genetic defect breeds truly in families, and no difference in the sex ratio has been noticed (19, 78, 102). Several forms of this disorder, congenital adrenal hyperplasia, are now recognized. The clinical manifestations in these variants depend upon the site of the metabolic block in the biosynthetic pathway, the severity of the defect, the sex of the subject, and the time of onset of the disorder.

Most frequently there is a partial impairment in the biosynthesis of cortisol. Hypersecretion of ACTH in an attempt to maintain homeostasis with respect to cortisol results in increased adrenocortical activity and consequent hyperplasia. The increased concentration of the intermediates immediately before the metabolic block may maintain a near normal cortisol secretion rate; these intermediates are released into the blood also, and their characteristic metabolites are excreted in the urine in excessive amounts. The clinical manifestations may arise from a relative deficiency of cortisol or aldosterone and from an excessive secretion of other steroids. The age at which the disease is manifest appears to be determined by the extent and site of the metabolic defect. The following variants of congenital adrenal hyperplasia have been observed:

1. Lipoid Adrenal Hyperplasia as a result of a defect in the biosynthesis of pregnenolone from cholesterol.
2. Defect in the oxidation of pregnenolone to progesterone caused by a deficiency of 3 β-hydroxysteroid dehydrogenase.
3. 17α-hydroxylase deficiency.
4. C-21 hydroxylase deficiency. There are two types of this disorder, viz., salt-losing and nonsalt-losing. In salt-losing patients biosynthesis of aldosterone is also affected. In nonsalt-losing patients only the biosynthesis of cortisol is affected. Three different hypotheses have been advanced to explain this difference.
5. 11β-hydroxylase deficiency. Two kinds of this disorder—the hypertensive type (probably due to an excessive secretion of 11-deoxycorticosterone) and the normotensive type—have been reported.
6. Defect in aldosterone biosynthesis only.

Genetic defect in the conversion of 18-hydroxycorticosterone to aldosterone has been specifically reported (99). A defect in C-18 hydroxylation of corticosterone has also been suggested (102).

These metabolic defects and the enzymes involved have been discussed in some detail earlier. In the following section, effects of a partial or almost total deficiency of these enzymes on the secretion of various steroids and their concentrations in the blood are studied by simulating these metabolic blocks of various enzyme reactions. In simulating a partial block the maximum velocity of the enzyme reaction has been considered to be one-tenth of normal; a maximum velocity of one-thousandth of normal has been used to simulate the conditions of a total block. All other parameters have been kept the same as in the normal case. In the case of the C-21 hydroxylation defect, two hypotheses have been simulated: that the nonsalt-losing variant results from a less severe block of C-21 hydroxylation, and that the hydroxylation of both progesterone and 17α-hydroxyprogesterone is blocked. Two situations have been considered: (a) when compared to the normal, hydroxylation of progesterone is one-tenth and that of 17α-hydroxyprogesterone is one-thousandth; (b) when the comparative blocks in the hydroxylation of these substrates have been reversed.

The effects of blocking various enzyme reactions of the biosynthetic chain have been summarized in Tables IV to IX. The effects of administering ACTH and cortisol under these simulated conditions have also been studied and are shown in Figures 7 to 13.

Simulation of Liver Disorder Affecting Cortisol Metabolism

The liver is the organ primarily responsible for the metabolism of steroid hormones (84). Because of this role, it might be expected that this organ could indirectly influence the synthesis of corticosteroids by the adrenals. Plasma 17-hydroxycorticosteroid levels have been found to be normal in cirrhosis of the liver, but infused cortisol disappears at a decreased rate in patients with hepatitis or cirrhosis (34). In patients with liver disease, Peterson (76) observed normal plasma levels of cortisol and corticosterone but found urinary corticoids and 17-ketosteroids to be below the normal level. Although several other infused steroids were metabolized at a normal rate, cortisol was metabolized at a diminished rate. The rate of the biosynthesis of cortisol and corticosterone was also markedly reduced in patients with cirrhosis. It was suggested that a homeostatic mechanism through the liver-pituitary-adrenals leads to a decreased synthesis of cortisol and corticosterone in patients with

TABLE IV

Simulation of Hydroxysteroid Dehydrogenase Defect (Reaction 3 blocked)

Effects of the administration of cortisol are shown in Figure 7.

	Total Block: V_{max} = Normal/1000		Partial Block: V_{max} = Normal/10	
	Blood Conc. per liter	Secretion Rate per day	Blood Conc. per liter	Secretion Rate per day
ACTH	0.53 m un	6.25 IU	0.412 m un	4.84 IU
Cortisol	0.151×10^{-8} M	0.072 mg	0.116×10^{-6} M	5.55 mg
Aldosterone	0.706×10^{-11} M	0.63×10^{-3} mg	0.52×10^{-9} M	0.0466 mg
Androgen (Δ^4-Dione)	0.626×10^{-9} M	0.629×10^{-2} mg	0.132×10^{-8} M	0.491 mg
11β-OH-Δ^4-Dione	—	0.0121 mg	—	0.945 mg
Pregnenolone	0.851×10^{-7} M	27.2 mg	0.662×10^{-7} M	21.5 mg
	Amount in Adrenal			
20α-OH-CHOL.	0.635×10^{-7} M/l		0.691×10^{-7} M/l	

TABLE V

*Simulation of 17α-Hydroxylase Defect**

(Reaction 4 blocked) and Simulation of a Multiple Defect Involving Hydroxylations at C-11 as well as C-17 (Reactions 4 and 22 blocked). Effects of the administration of cortisol are given in Figures 8 and 9.

	Reaction 4 blocked		Reactions 4 and 22 blocked			
	For Prog. to 17α-OH-Prog. V_{max} Normal/1000		For Prog. to 17α-OH-Prog. V_{max} – Normal/1000 For Prog. to DOC: V_{max} Normal/1000		For Prog. to 17α-OH-Prog. V_{max} Normal/10 For Prog. to DOC: V_{max} – Normal/1000	
	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day
ACTH	5.29 m un	6.20 IU	5.20 m un	6.07 IU	3.20 m un	3.75 IU
Cortisol	0.579×10^{8} M	0.274 mg	0.108×10^{-7} M	0.590 mg	0.480×10^{6} M	19.5 mg
ALDO	0.717×10^{8} M	0.638 mg	0.354×10^{-8} M	0.316 mg	0.189×10^{10} M	0.169×10^{-2} mg
Δ^4-Dione	0.651×10^{9} M	0.0246 mg	0.691×10^{-9} M	0.052 mg	0.312×10^{-8} M	1.75 mg
11β-OH-Δ^4-Dione	—	0.0472 mg	—	0.100 mg	—	3.32 mg
Prog.	0.191×10^{6} M	13.8 mg	0.514×10^{6} M	37.4 mg	0.131×10^{6} M	9.45 mg
17α-OH-Prog.	0.606×10^{-10} M	0.0701 mg	0.115×10^{-9} M	0.152 mg	0.439×10^{8} M	5.21 mg
			Amount in Adrenal			
DOC	$.261 \times 10^{5}$ M/*l*		0.436×10^{6} M/*l*		0.145×10^{8} M/*l*	
Corticosterone	$.230 \times 10^{6}$ M/*l*		0.464×10^{7} M/*l*		0.157×10^{9} M/*l*	

* References: Biglieri (1966); Neher and Peterson (1967)

TABLE VI

*Simulation of C-21 Hydroxylase Defect: Non-Salt Losing Hypothesis C** (See page 8)—
Only cortisol biosynthesis affected

(Reaction 5 blocked. Effect of cortisol administration shown in Figure 10)

	Total block V_{max} = Normal/1000		Partial block V_{max} = Normal/10	
	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day
ACTH	5.34 m un	6.25 IU	5.61 m un	5.41 I.U.
Cortisol	0.148×10^{-8} M	0.07 mg	0.100×10^{-6} M	5.86 mg
Aldosterone	0.211×10^{-8} M	0.188 mg	0.191×10^{-8} M	0.176 mg
Androgen (Δ^4-Dione)	0.107×10^{-7} M	7.0 mg	0.836×10^{-8} M	5.41 mg
11β-OH-Δ^4-Dione	—	12.9 mg	—	10.1 mg
Progesterone	0.162×10^{-7} M	1.17 mg	0.141×10^{-7} M	1.07 mg
17α-OH-Prog.	0.177×10^{-7} M	20.3 mg	0.103×10^{-7} M	15.9 mg
DOC (in adrenal)	0.207×10^{-6} M	—	0.189×10^{-6} M	—
Corticosterone (in adrenal)	0.223×10^{-7} M	—	0.205×10^{-7} M	—

* References: Bartter et al 1968; Visser 1966; Bryan et al 1965; Kowarski et al 1965; Fukushima et al 1961.

TABLE VII

*Simulation of C-21 Hydroxylase Defect: Hypothesis B** (See page 8)—*Cortisol as well as aldosterone biosynthesis is affected, but aldosterone production is compensated.*

(Reactions 5 and 22 blocked. Effects of the administration of ACTH and cortisol are shown in Figure 11)

	For 17α-OH-Prog V_{max} = Normal/1000 For Prog V_{max} = Normal/10		For 17α-OH-Prog V_{max} = Normal/10 For Prog V_{max} = Normal/1000	
	Blood Conc. per lit.	Secretion rate per day	Blood Conc. per lit.	Secretion rate per day
ACTH	5.32 m un	6.25 IU	4.52 m un	5.25 IU
Cortisol	0.168×10^{-8} M	0.079 mg	0.128×10^{-7} M	6.51 mg
Aldosterone	0.275×10^{-9} M	0.0245 mg	0.269×10^{-11} M	0.242×10^{-3} mg
Androgen (Δ^4-Dione)	0.113×10^{-7} M	7.48 mg	0.939×10^{-8} M	6.03 mg
11β-OH-Δ^4-Dione	—	10.75 mg	—	8.79 mg
Progesterone	0.173×10^{-7} M	1.25 mg	0.155×10^{-7} M	1.20 mg
17α-OH-Prog.	0.189×10^{-7} M,	21.9 mg	0.153×10^{-7} M	17.8 mg
DOC (in adrenal)	0.215×10^{-7} M	—	0.209×10^{-9} M	—
Corticosterone (in adrenal)	0.234×10^{-8} M	—	0.225×10^{-10} M	—

* Eberlein and Bongiovanni: J Clin Invest 37:889, 1958 and Pediatrics 21:661, 1958.

liver disease in whom the rate of cortisol catabolism is impaired.

While the secretion of cortisol, corticosterone, and adrenal androgens is frequently suppressed in liver disease, aldosterone production appears to remain normal (27). The half-life of cortisol has been found to range from 190–330 min. (normal about 90 min.) and that of corticosterone from about

TABLE VIII

Simulation of 11β-Hydroxylase Defect

(Reaction 7 or 7 and 23 blocked) Effects of the administration of cortisol are shown in Figure 12.

	Reaction 7		Reactions 7 and 23		For 11-deoxycortisol	
	For 11-deoxycortisol: V_{max} = Normal/1000		For 11-deoxycortisol: V_{max} = Normal/1000 For DOC: V_{max} = Normal/10		V_{max} = Normal/10 For DOC: V_{max} = Normal/1000	
	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day
ACTH	5.35 m un	6.24 IU	5.35 m un	6.24 IU	0.379 m un	4.42 m un
Cortisol	0.213×10^{-8} M	0.103 mg	0.213×10^{-8} M	0.103 mg	0.241×10^{-6} M	10.0 mg
ALDO	0.211×10^{-8} M	0.188 mg	0.211×10^{-8} M	0.108 mg	0.108×10^{-9} M	0.009 mg
Δ^4-Dione	0.404×10^{-8} M	2.39 mg	0.404×10^{-8} M	2.39 mg	0.376×10^{-8} M	2.19 mg
11β-OH-Δ^4-Dione	—	4.54 mg	—	4.54 mg	—	4.16 mg
Prog.	0.162×10^{-7} M	1.17 mg	0.162×10^{-7} M	1.17 mg	0.148×10^{-7} M	1.07 mg
11-Deoxycortisol	0.102×10^{-5} M	25.8 mg	0.102×10^{-5} M	25.8 mg	0.566×10^{-6} M	14.2 mg
DOC (in adrenal)	0.207×10^{-6} M	—	0.256×10^{-5} M	—	0.357×10^{-3} M	—
Corticosterone	0.268×10^{-5} M	—	0.268×10^{-5} M	—	0.902×10^{-9} M	—

References: Chaptal et al 1959; Bergstrand et al 1959; Eberlein and Bongiovanni 1955; Gabrilove et al 1965.

84–102 min. (normal about 20 min) in patients with liver disease. The effects of increased half-life of cortisol has been simulated and the results are shown in Table X.

Parameter Sensitivity Studies

One important task a computer model of a system can accomplish is to determine the relative influence of various system parameters on particular system properties. Parameter sensitivity, as this is called, affects model construction, parameter identification procedures, and, very significantly, design of experiments to be carried out on the actual system. In general, the purpose of an experiment is to infer the value of one or more parameters from the measurement of other quantities, usually state variables. Since it is usually impossible to measure all of the state variables, a parameter sensitivity study carried out on a model can indicate to the experimenter which measurements have the strongest bearing on the parameter he is looking for. Such a study can also demonstrate the need for further experimentation, for example, when a parameter which has a strong influence on the system output is not well known.

The changes in steady-state concentrations of some of the important hormones due to changes in various parameters are shown in Table XI. It is interesting that the table reveals one aspect of the basic regulatory mechanism: the rises or falls in cortisol concentration caused by the parameter changes are partially offset by opposite changes in the ACTH concentration. The last two rows of the table imply that the value of V_7 has no effect at all on

TABLE IX

Simulation of Defects in Aldosterone Biosynthesis Only

(Reaction 22 or 23 or 25 blocked) Effects of the administration of ACTH or cortisol are shown in Figures 12a, 12b, and 12c, respectively

	Reaction 22*		Reaction 23**		Reaction 25	
	Prog. to DOC blocked V_{max} = Normal/1000		DOC to Corticosterone blocked V_{max} = Normal/1000		Corticosterone to ALDO blocked V_{max} = Normal/1000	
	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day	Blood Conc. per liter	Secretion rate per day
ACTH	2.97 m un	3.44 IU	0.3 m un	3.5 IU	0.3 m un	3.5 IU
Cortisol	0.589×10^{-6} M	24.0 mg	0.562×10^{-6} M	22.8 mg	0.562×10^{-6} M	22.8 mg
ALDO	0.242×10^{-11} M	0.216×10^{-3} mg	0.187×10^{-8} M	0.166 mg	0.197×10^{-11} M	0.175×10^{-3} mg
Δ^4Dione	0.375×10^{-8} M	2.19 mg	0.355×10^{-8} M	2.05 mg	0.355×10^{-8} M	2.5 mg
11β-OH-Δ^4-Dione	—	4.15 mg	—	3.98 mg	—	3.98 mg
Progesterone	0.148×10^{-7} M	1.07 mg	0.139×10^{-7} M	1.0 mg	0.139×10^{-7} M	1.0 mg
DOC (in adrenal)	0.185×10^{-9} M	—	saturated*	—	0.177×10^{-6} M	—
Corticosterone (in adrenal)	0.200×10^{-10} M	—	0.9×10^{-9}	—	0.204×10^{-7} M	—

* References: Bryan et al 1965; Kowarski et al 1965; Eberlein and Bongiovanni 1955, 1956; Kowarski et al 1968; Visser and Cost 1964; Ulick, Nicolis and Vetter 1964.

** This reaction saturates with V_{max} = Normal/1000, but the concentrations and secretion rates do not reflect this since no outlet to the blood was allowed for DOC in the model.

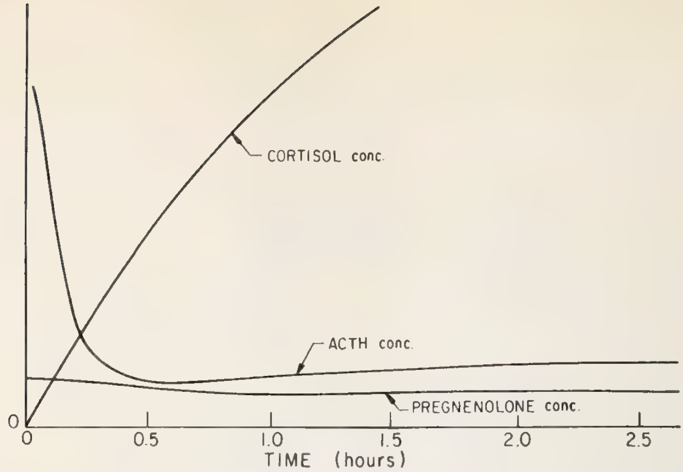

FIG. 7. Simulation of Hydroxysteroid Dehydrogenase Defect Reaction 3 blocked (20α-OH-Chol→Pregnenolone) V_{max} one thousandth of normal, cortisol infused at four times normal rate.

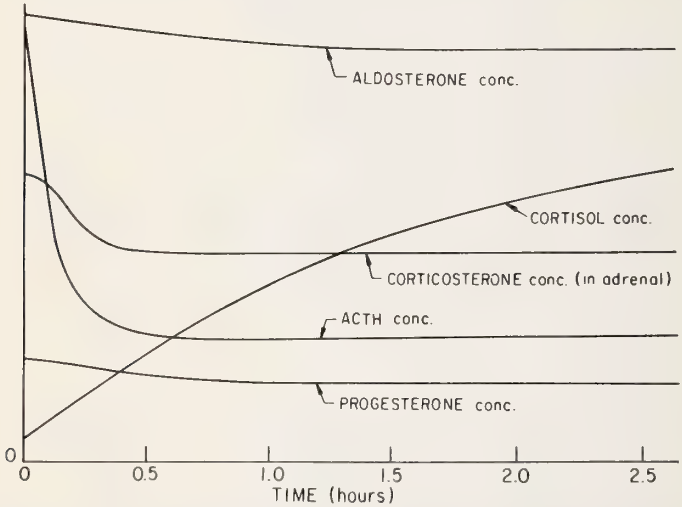

FIG. 8. Simulation of 17α-Hydroxylase Defect Reaction 4 blocked (PROG→17α-OH-PROG, V_{max} one-thousandth of normal, cortisol infused at twice normal rate.

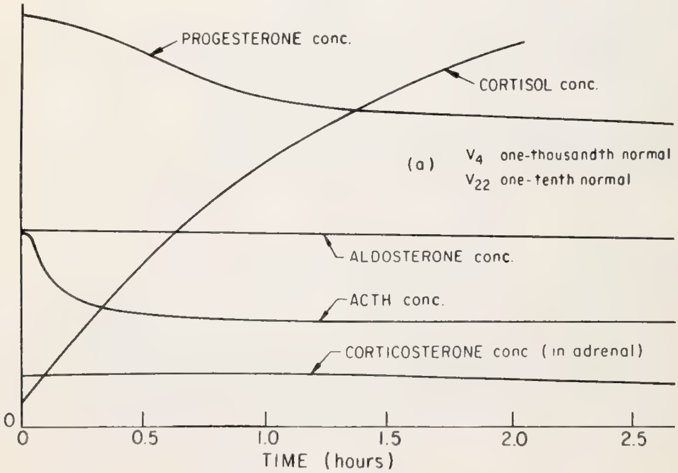

FIG. 9a. Simulation of a Multiple Defect Involving Hydroxylations at C-11 as well as C-17. Reactions 4(PROG→17α-OH-PROG) and 22(PROG→DOC) blocked. Cortisol infused at four times normal rate. (a) V_{22} = one-tenth of normal, V_4—one-thousandth of normal.

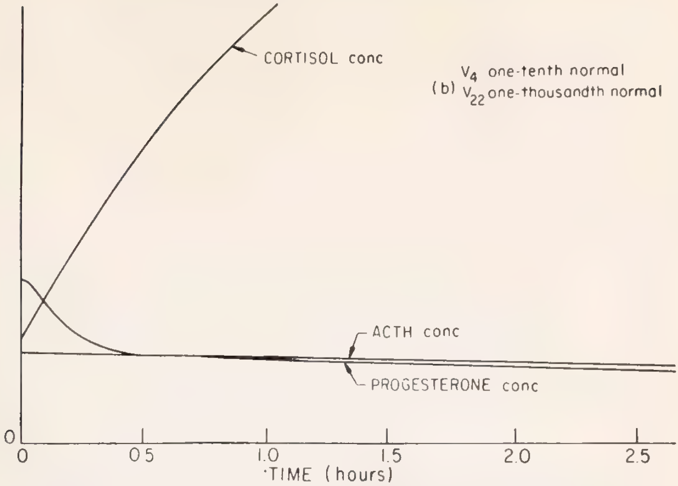

FIG. 9b. (b) V_{22}—one thousandth normal, V_4—one-tenth normal.

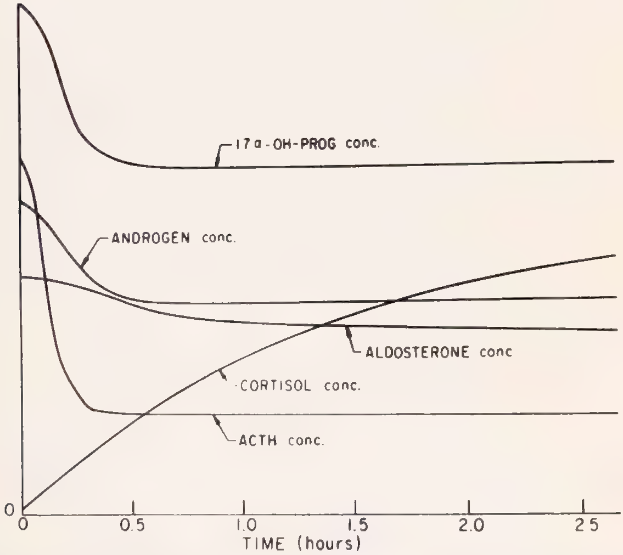

FIG. 10. Simulation of C-21 Hydroxylase Defect: Non-Salt Losing. Reaction 5 blocked (17α-OH-PROG →11-DEOXY-CORT). $V_{\max}$ one-thousandth of normal. Cortisol infused at twice normal rate.

the steady-state solution. This is because the adrenal concentration of 11-deoxycortisol (which diffuses into the blood very slowly) rises (or falls) just enough to maintain the cortisol concentration level. Findings of this sort are good examples of the interaction of model building and experimentation. In this case better fixes could be obtained on many of the system parameters if more data were available on hormone concentrations in the adrenal.

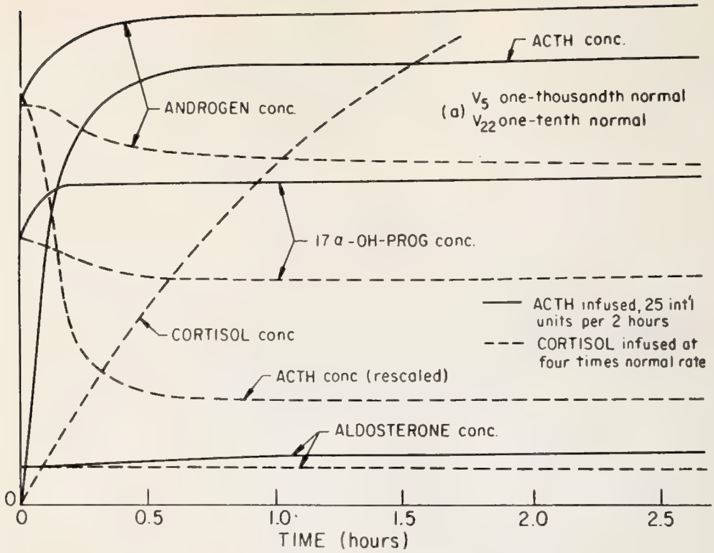

FIG. 11a. Simulation of C-21 Hydroxylase Defect: Hypothesis B (See page 8). Reactions 5(17α-OH-PROG→11-DEOXY-CORT) and 22(PROG→DOC) blocked. (a) V_5 one-thousandth normal, V_{22} one-tenth normal.

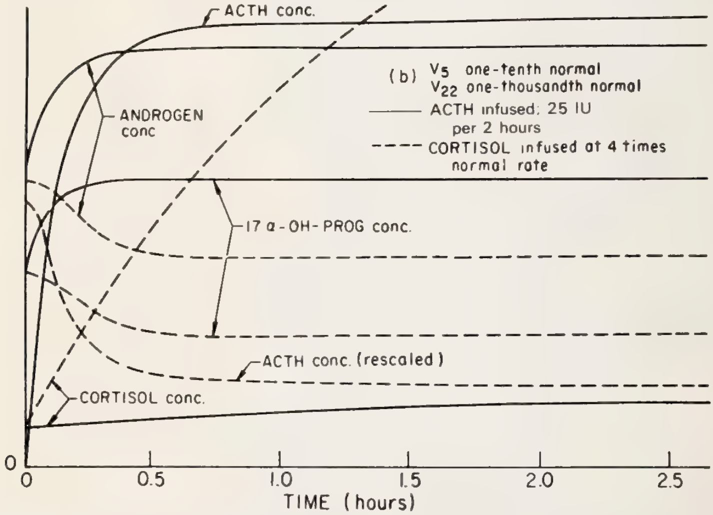

FIG. 11b. ACTH infused, 25 Int'l units per 2 hours Cortisol infused, four times normal rate (b) V_5—one-tenth normal.

Two dynamic studies were also made as part of the parameter sensitivity study. In Figure 14, the effect of a change in KPR is shown. As expected, there are changes both in the initial state and in the dynamics. In the second case (Fig. 15) KPR and KAC were changed simultaneously in such a way that the initial state did not change at all. The resulting purely dynamic change in the system response could not have been detected from steady-state studies. As

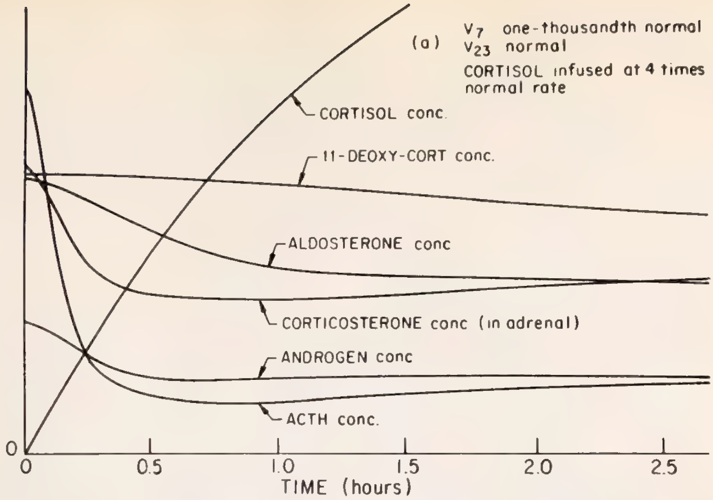

FIG. 12a. Simulation of 11β-Hydroxylase Defect (a) V_7 – one-thousandth normal, V_{23} = normal. Cortisol infused at 4 times normal rate.

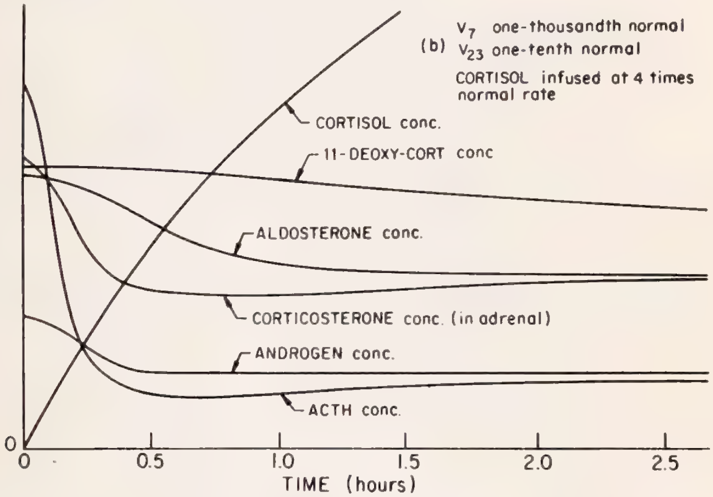

FIG. 12b. (b) V_7 = one-thousandth normal, V_{23} = one-tenth normal. Cortisol infused at 4 times normal rate.

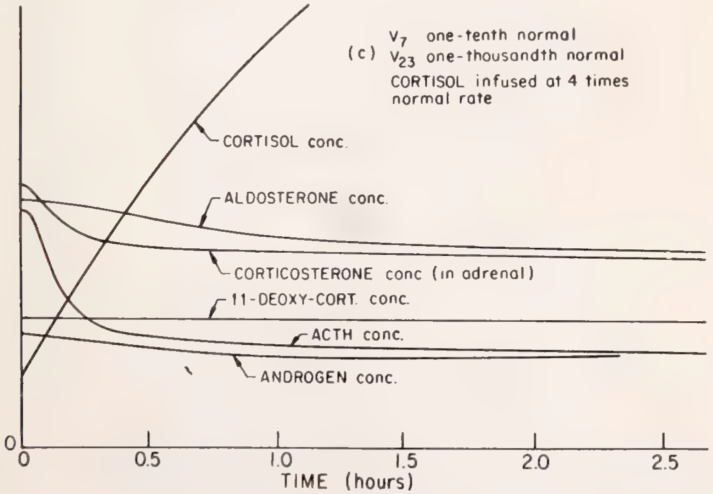

FIG. 12c. (c) V_7 = one-tenth normal, V_{23} = one-thousandth normal. Cortisol infused at 4 times normal rate.

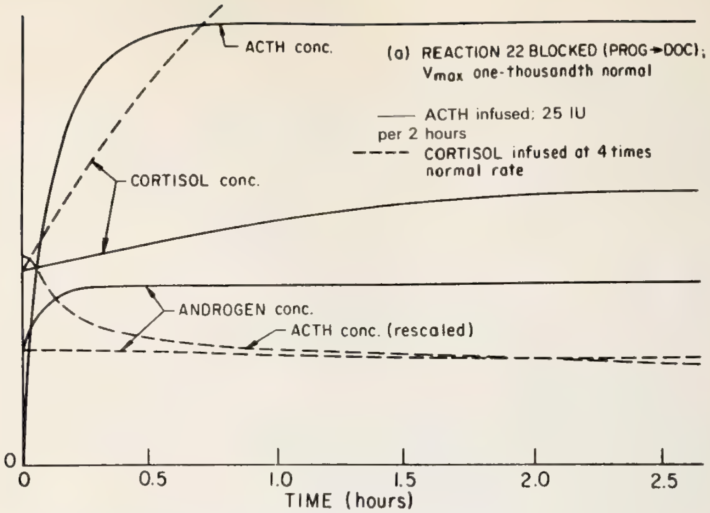

FIG. 13a. Simulation of Defects in Aldosterone Biosynthesis Only (a) Reaction 22 blocked (PROG→DOC), V_{max} one-thousandth of normal.

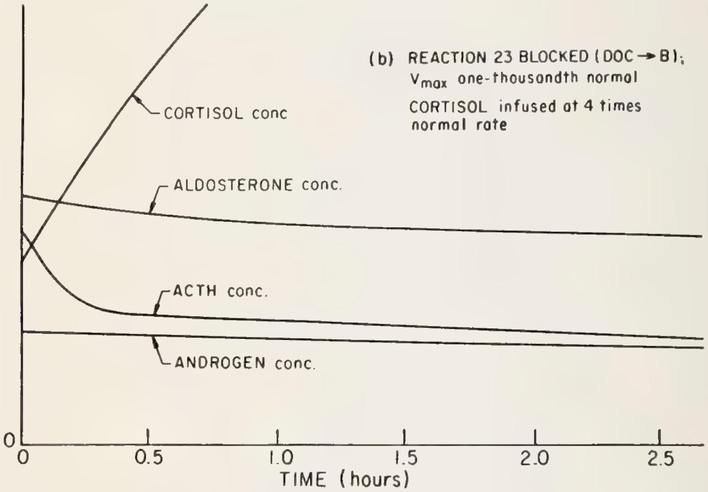

FIG. 13b. Reaction 23 Blocked (DOC→B); V_{max} one-thousandth of normal. Cortisol infused at 4 times normal rate.

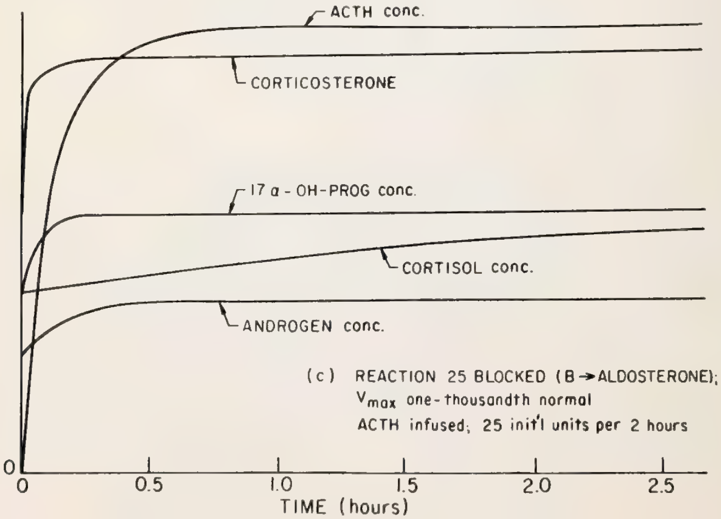

FIG. 13c. Reaction 25 Blocked (B→Aldosterone) V_{max} one-thousandth of normal ACTH in-

TABLE X

Simulation of Change in Cortisol Half-Life

	Normal ($t_{1/2}$ = 70 min)		Increased Half-Life ($t_{1/2}$ = 140 min)	
	Blood Conc. per liter	Secretion Rate per day	Blood Conc. per liter	Secretion Rate per day
ACTH	0.3 m un	3.5 IU	0.221 m un	2.59 IU
Cortisol	0.562×10^{-6} M	22.8 mg	0.990×10^{-6} M	20.7 mg
Aldosterone	0.187×10^{-8} M	0.166 mg	0.171×10^{-8} M	0.153 mg
Δ^4-Dione	0.355×10^{-8} M	2.05 mg	0.328×10^{-8} M	1.86 mg
11β-OH-Δ^4-Dione	—	3.98 mg	—	3.53 mg
Corticosterone (in adrenal)	0.191×10^{-7} M	—	0.173×10^{-7}	—

TABLE XI

Parameter Sensitivity Studies, Summary of Results—Steady-State Case

Parameter	Change from Normal %	Changes in Steady-State Concentration (Percent)			
		Cortisol	ACTH	Aldosterone	Δ^4-Dione
KAC	−50	+18	−7.4	+14	+15
KAC	+100	−15	+8.4	−16	−16
KPR	−50	−18	+9.5	−14	−16
KPR	+100	+21	−8.5	+15	+16
V_4	−50	−6.0	+3.2	+59	−6.1
V_4	+100	+2.7	−1.5	−43	+3.7
V_5	+100	+18	−6.3	−2.7	−34
V_7	50	0	0	0	0
	+100	0	0	0	0

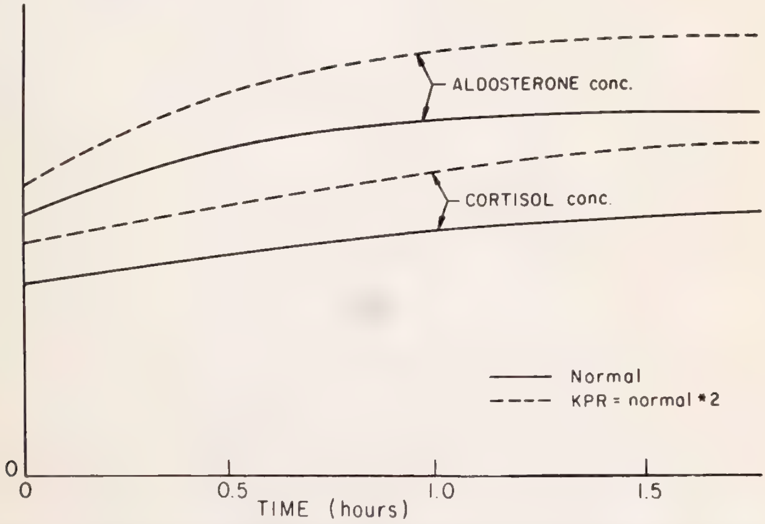

FIG. 14. Parameter Sensitivity Studies; ACTH infusion; 25 Int'l units per 2 hours.

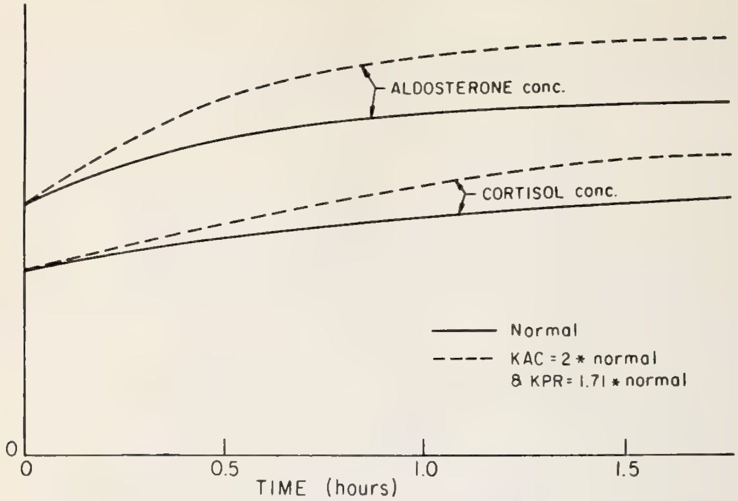

FIG. 15. Parameter Sensitivity Studies ACTH infusion; 25 Int'l units over 2 hours.

noted earlier, changes of a purely dynamic nature have not yet been included in the parameter identification.

Acknowledgment

Professor David Auslander's help concerning the model in this study is gratefully acknowledged.

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